

CARCINOMA OF THE THYROID

Preoperative Diagnosis and Prognostic Factors

Jan Tennvall



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Title and subtitle CARCINOMA OF THE THYROID. Preoperative Diagnosis and Prognostic Factors.			
Abstract By improving preoperative diagnosis and identification of important prognostic factors of thyroid carcinoma (TC) it might be possible to decrease the number of diagnostic surgical interventions and to give patients with a confirmed TC a more adequate treatment. <i>Preoperative diagnosis:</i> Consecutive series of 83 patients with scintigrams and of 203 patients with fine-needle aspiration (AC) with subsequently histologically confirmed TC were evaluated as well as 217 patients with confirmed benign thyroid disorders. The most common scintigraphic appearance was a solitary reduced uptake (70 %). The minimum detectable size of TC with this feature was 10 mm apart from medullary TC. False positive AC was rare (1.8 %), thus the specificity of AC was high (0.98). The sensitivity of AC for medullary and undifferentiated TC was 0.82-0.84, but it was for papillary (occult TC excluded) 0.58 and for follicular TC 0.42. A 'cold' nodule with also a decreased thallium-uptake is mostly a benign disorder, but with an increased uptake it might be a well-differentiated TC or a follicular adenoma. These could, however, be significantly separated by the thallium-elimination rate ($p=0.0001$) and thereby it was possible to divide the patients in a high-risk group (11/23 with TC) and a low-risk group (5/34 with TC). In vitro NMR-measurements (T1- and T2-values) showed to reflect different thyroid tissue components. <i>Prognostic factors:</i> During 1955-1972, 262 patients with histologically verified TC were referred to the Department and 226 of these (86 %) with a median follow-up of 11 years form the basis for prognostic multivariate analyses. According to these analyses, and when deaths in intercurrent disease were estimated, neither age at diagnosis nor sex were found to be important predictors of survival of TC. Thus, the EORTC-prognostic index could not be reproduced. The following predictors were identified: for papillary TC: tumour extension beyond the thyroid capsule and marked cellular atypia; for follicular TC: tumour extension beyond the thyroid capsule, marked cellular atypia and distant metastases; for medullary TC: tumour extension beyond the thyroid capsule. (Distant metastases were not evaluated for papillary or medullary TC, due to the small number of patients with this characteristic).			
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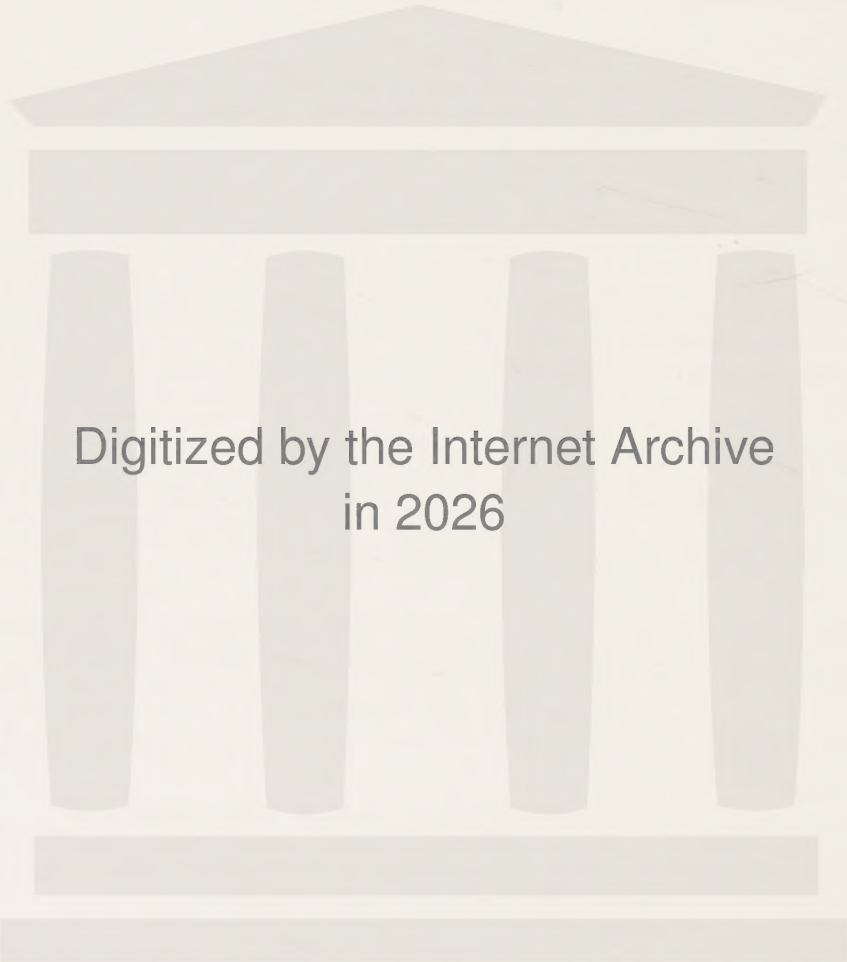
Signature Jan Tennvall

Date 9 April, 1984

PAPERS I-VII

Apart from certain unpublished results, this thesis is based upon the following papers, which will be referred to in the text by their Roman numerals:

- I. Tennvall J, Cederquist E, Möller T, Naversten Y and Åkerman M.
PREOPERATIVE SCINTIGRAPHY WITH CORRELATION TO CYTOLOGY AND HISTO-
PATHOLOGY IN CARCINOMA OF THE THYROID.
Acta Radiologica Oncology 22:183-191, 1983.
- II. Åkerman M, Tennvall J, Biörklund A, Mårtensson H and Möller T.
SENSITIVITY AND SPECIFICITY OF FINE-NEEDLE ASPIRATION CYTOLOGY IN
THE DIAGNOSIS OF TUMOURS OF THE THYROID GLAND.
Submitted for publication.
- III. Tennvall J, Palmer J, Cederquist E, Larsson I, Biörklund A, Ingemans-
son S and Åkerman M.
SCINTIGRAPHIC EVALUATION AND DYNAMIC STUDIES WITH THALLIUM-201 IN
THYROID LESIONS WITH SUSPECTED CANCER.
European Journal of Nuclear Medicine 6:295-300, 1981.
- IV. Tennvall J, Palmer J, Biörklund A, Möller T, Ranstam J and Åkerman M.
KINETICS OF ^{201}Tl UPTAKE IN ADENOMAS AND WELL-DIFFERENTIATED CARCI-
NOMAS OF THE THYROID. A DOUBLE ISOTOPE INVESTIGATION WITH $^{99}\text{Tc}^{\text{m}}$ AND
 ^{201}Tl .
Acta Radiologica Oncology (In press).
- V. Tennvall J, Biörklund A, Möller T, Olsson M, Persson B and Åkerman M.
STUDIES OF NMR-RELAXATION-TIMES IN MALIGNANT TUMOURS AND NORMAL
TISSUES OF THE HUMAN THYROID GLAND.
In: Progress in Nuclear Magnetic Resonance, Vol 8, S Karger AG, Basel
(In press).
- VI. Tennvall J, Biörklund A, Möller T, Ranstam J and Åkerman M.
IS THE EORTC-PROGNOSTIC INDEX OF THYROID CANCER VALID IN DIFFERENTI-
ATED THYROID CARCINOMA? RETROSPECTIVE MULTIVARIATE ANALYSIS OF DIF-
FERENTIATED THYROID CARCINOMA WITH LONG FOLLOW-UP.
Submitted for publication.
- VII. Tennvall J, Biörklund A, Möller T, Ranstam J and Åkerman M.
PROGNOSTIC FACTORS OF PAPILLARY, FOLLICULAR AND MEDULLARY CARCINOMAS
OF THE THYROID GLAND. RETROSPECTIVE MULTIVARIATE ANALYSIS OF 221 PA-
TIENTS WITH A FOLLOW-UP OF 11 YEARS.
Submitted for publication.



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PAPERS I-VII

INTRODUCTION

The proper management of a thyroid nodule is still a controversial issue after decades of discussion (De Groot 1974, Greer 1974). The discovery of a solitary thyroid nodule at clinical examination is, however, a common sign (Vander et al. 1968, Borup Christensen et al. 1984), while a clinical thyroid carcinoma is an uncommon disease with an approximate incidence of 2.5×10^{-5} for males and 6.0×10^{-5} for females (Cancer Incidence in Sweden, 1980). On the other hand a solitary nodule is often the first and only sign of a thyroid carcinoma.

Even in well-selected surgical series of solitary thyroid nodules the lesion is found to be benign in about 80 per cent of the cases (Dische et al. 1964, Kendall and Condon 1969, Alderson et al. 1976, Burrow et al. 1978). There is still thus a need for improvement in the selection of patients for surgery (diagnostic lobectomy) which would spare patients unnecessary operations that sometimes imply the risk for complications and/or inconvenience for the patient, and expenses both for the patient and the community.

Thyroid carcinomas constitute a heterogenous group of tumours with varying prognoses and biologic behavior. The histopathologic classification of these tumours proposed by WHO (Hedinger and Sobin 1974, Table I) reflects to a great extent these differences (Woolner et al. 1961, 1971).

TABLE I. WHO classification of malignant epithelial thyroid tumours.

-
1. Follicular carcinoma
 2. Papillary carcinoma
 3. Squamous cell carcinoma
 4. Undifferentiated (anaplastic) carcinoma
 - a. Spindle cell type
 - b. Giant cell type
 - c. Small cell type
 5. Medullary carcinoma
-



Follicular and papillary carcinomas (well-differentiated carcinomas), which account for the majority of malignant thyroid tumours, are known to usually have a good prognosis or an indolent course (Cady et al. 1979), but some of

these tumours also have a fatal course (Tscholl-Ducommun and Hedinger 1982, Ladurner et al. 1983). By identifying important prognostic factors for these histologic groups it might be possible to give patients with poor prognoses an aggressive treatment, but also to avoid 'overtreatment' of patients with favourable prognoses. Age at diagnosis, the patient's sex or the extent of the primary tumour are some of the many prognostic factors proposed (Woolner et al. 1961, 1971, Cady et al. 1979, Tscholl-Ducommun and Hedinger 1982). Several of these are, however, significantly correlated to each other (VI, VII), which makes it more difficult to evaluate the prognostic significance of each factor.

Squamous cell carcinoma of the thyroid is an extremely rare tumour (Huang and Assor 1971). In the present studies no tumour of this type was identified.

Undifferentiated carcinomas of giant or spindle cell type are usually considered as one group (large cell carcinoma). The prognosis is dismal, despite aggressive treatment. The median survival is usually about 6 months and most of the patients are dead within a year after the diagnosis has been established (Aldinger et al. 1978, Tennvall et al. 1979, Werner et al. In press). As almost all patients with this histologic type have very poor prognoses, other possible prognostic factors have not been evaluated in the present study. Discrete anaplastic foci have not been found in any specimen of the differentiated carcinomas included in the present prognostic studies.

It is becoming generally accepted that most *anaplastic carcinomas of small cell type* are malignant lymphomas. It has also been shown that these tumours can be sub-classified according to modern non-Hodgkin lymphoma classification (Heiman et al. 1978, Åkerman et al. unpublished data), and that this classification is a good predictor (Heiman et al. 1978).

The prognosis of *medullary carcinomas* is not very well evaluated in comparison with papillary, follicular and large cell carcinomas, partly because most reports are based on rather small patient-materials, and partly because it was first described as a clinicopathologic entity as late as in 1959 (Hazard et al. 1959). It is generally believed that all medullary carcinomas are derived from the parafollicular cells (C-cells), but recent reports have cast doubt on the validity of this concept (Hales et al. 1982, Ljungberg et al. 1983, Caillou et al. 1983).

The term 'differentiated thyroid carcinomas', used in the present study, is a collective concept of papillary, follicular, and medullary carcinomas.

EPIDEMIOLOGICAL CONSIDERATIONS AND BACKGROUND DATA

The Southern Swedish Health Care Region, which is served by the Department of Oncology, University Hospital, Lund, comprises the counties of Kronoberg (G), Blekinge (K), Kristianstad (L), Malmöhus (M) and the southern part of the county of Halland (N). Until 1960, the southern part of the county of Kalmar (H) was also included. Patients diagnosed in the community of Malmö, the county of Malmöhus, are treated at Malmö General Hospital, and are thus not referred to the Department in Lund.

The population was in 1965 1.17 million (excluding the population of Malmö). Between 11-15 per cent of the population were found in each of the first seven decades of life, and 11 per cent were older than 70 years.

The National Swedish Cancer Registry was founded in 1958. The reporting of all new cases of cancer is compulsory. Between 1976 and 1982, the processing of cancer reports was regionalized. The Regional Tumour Registry (RTR) for southern Sweden, established in 1978, thus forms a population-based cancer registry containing information on all new cases of cancer occurring in the entire region since 1958.

A total of 498 cases of diagnosed malignant thyroid tumours was reported to the Regional Tumour Registry from the catchment area during the period 1958-1972 (Table II), and 308 of these were referred to the Department of Oncology in Lund for further treatment and/or follow-up. From the county of Halland, however, some patients were referred to the University Hospital in Gothenburg.

The median age at diagnosis for the patients reported to the tumour registry was 60 years, and the female/male ratio was 2.9:1. Table II gives a survey of the referral-rates from each county during 1958-1972. In the group of referred patients the median age was 55 and the female/male ratio was 3.0:1. During the investigated period, there was a slight increase in the number of cases reported to the RTR, as well as in the number of patients referred to the Department (Fig 1). The referral-rates for all thyroid carcinomas as well as for papillary and follicular thyroid carcinomas are also given in Table II. The referral rates are certainly somewhat underestimated, since thyroid carcinomas diagnosed at autopsies are included in the figures of RTR.

TABLE II. Referral rate of patients to the Department of Oncology from the different Counties of Southern Swedish Health Care Region 1958-1972 (Community of Malmö excluded).

	County					N*	H	Other counties	Total number
	G	K	L	M					
All thyroid carcinomas	Diagnosed	67	57	98	210	66	-	-	498
	Referred	27 (40 %)	36 (63 %)	82 (84 %)	140 (67 %)	8 (12 %)	11	4	308
Papillary and follicular thyroid ca	Diagnosed	46	41	79	172	47	-	-	385
	Referred	16 (35 %)	26 (63 %)	54 (68 %)	103 (60 %)	5 (11 %)	6	4	214

*Northern part of the county of N is served by University Hospital, Gothenburg.

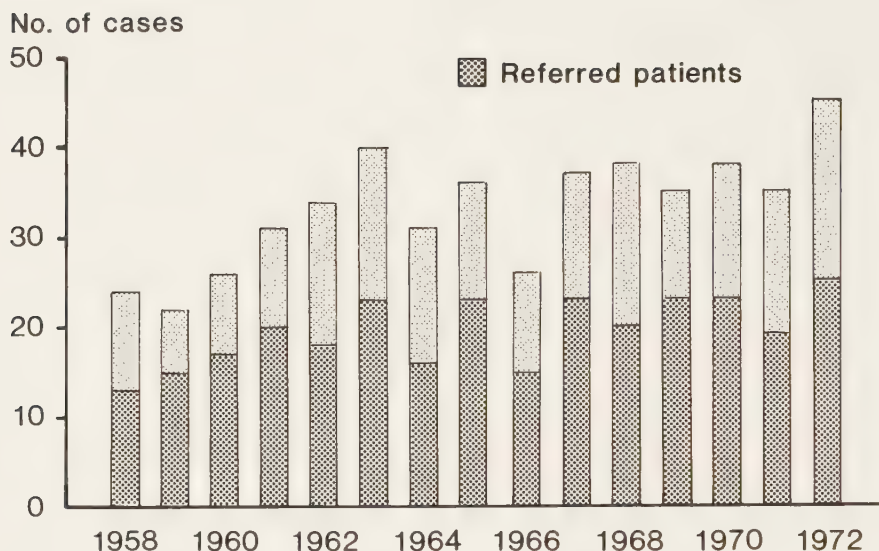


Figure 1. The annual referral rate of thyroid carcinomas 1958-1972 to the Department of Oncology from Southern Swedish Health Care Region (Community of Malmö excluded). The annual referral rate varied between 53 % and 68 %.

An estimation of the validity of the data in the RTR regarding the diagnosis of papillary and follicular carcinoma could be made from the re-examination of 88 per cent ($n=207$) of patients with these diagnoses, referred to the Department during the period studied (1955-1972, VI:Table I). Only 3 per cent ($n=7$) were found to be erroneously reported as carcinomas, the lesions being at re-examination classified as follicular adenomas. Occult carcinomas (≤ 10 mm) were found in 12 per cent ($n=28$) of re-examined well-differentiated carcinomas (papillary and follicular carcinomas).

A study of the reliability of the histologic classification of malignant thyroid tumours reported to the National Swedish Cancer Registry during 1958-1972 (Holm et al. 1980) disclosed benign thyroid lesions in 15 per cent of the cases reported from the Stockholm region and in 6 per cent of the cases reported from the rest of Sweden. The majority of the tumours (90 per cent) erroneously reported as carcinomas were designated as papillary or follicular carcinomas.

The coding of histology in the RTR does not distinguish medullary from undifferentiated carcinomas. Fifty-six per cent ($n=14$) of referred patients with medullary carcinomas during the period 1958-1972 came from the counties indicated G and L. It is well-known that there are many cases with familial medullary carcinomas in these two counties.

AIMS OF THE STUDY

By improving preoperative diagnosis and identification of important prognostic factors of thyroid carcinoma it might be possible to decrease the number of diagnostic surgical interventions and to give patients with a confirmed thyroid carcinoma a more adequate treatment. The specific aims of this study are:

1. To evaluate the scintigraphic appearance and detectability of thyroid carcinomas.
2. To evaluate the sensitivity and specificity of fine needle aspiration cytology in the diagnosis of thyroid carcinomas.
3. To define the indications of scintigraphic and dynamic studies with thallium-201 in the diagnosis of thyroid carcinomas.
4. To study the NMR-relaxation-times (T1- and T2-values) in relation to various types of thyroid tissues in vitro.
5. To identify prognostic variables predicting survival of patients with papillary, follicular, and medullary thyroid carcinomas.

MATERIALS

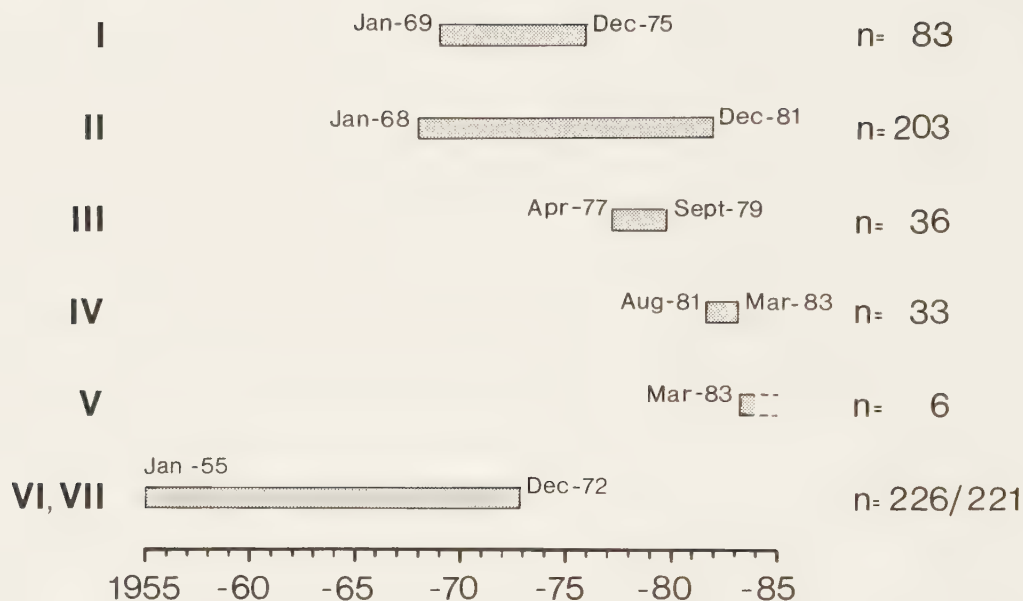


Figure 2. Chronological relation between patient-materials of studies I-VII.

Preoperative scintigraphy with iodine-131 and/or technetium-99m (I)

During the period 1969-1975, 83 out of 167 patients with thyroid carcinomas referred to or diagnosed at the Department of Oncology, University Hospital, Lund, fulfilled the following criteria: the presence of a preoperative scintigram of the thyroid and a histologic confirmation at total thyroidectomy or lobectomy. This material was used to correlate the different histologic types of thyroid carcinomas to the scintigraphic images and to assess scintigraphic detectability. A comparison with the results of preoperative aspiration cytology was also made.

Preoperative fine-needle aspiration cytology (II)

During the period 1968-1981, 203 patients with thyroid carcinomas were preoperatively investigated with fine-needle aspiration cytology (AC) at the Department of Cytodiagnostics, University Hospital, Lund. Patients with a cytological diagnosis obtained from lymph node or distant metastases, as well as patients with biochemically diagnosed medullary carcinomas with a

non-palpable thyroid gland, were not included. The material was used to estimate the sensitivity of AC in the diagnosis of a thyroid tumour and to evaluate the reason for a falsely negative AC. Also, all cases with a cellular atypia or indeterminate diagnosis were re-evaluated and analysed.

During the period 1980-1981, 217 patients with a histopathologically verified benign disease of the thyroid were also investigated preoperatively with AC at the Department of Cytodiagnostics. The specificity of AC of a thyroid mass was thus estimated, based on this material.

Scintigraphy and dynamic studies with thallium-201 (III, IV)

During the period April, 1977-September, 1979 (III), 46 patients, in whom the preoperative iodine or technetium scintigram showed a solitary area with reduced uptake or no uptake at all, were further investigated with thallium-201 chloride. The final diagnosis was established in all patients by histology. The material was partly used for a scintigraphic evaluation of thallium-201 comprising all of these 46 patients (III:Table I), and partly for a dynamic study with the same radionuclide, initially comprising 41 of these 46 patients. In 36 patients, a region of interest could be identified, and it was therefore possible to evaluate these patients. The dynamic study included 5 papillary and 2 follicular carcinomas, 22 follicular adenomas and 7 nodular goitres.

During the period August, 1981-March, 1983 (IV), 33 patients with a histopathologically verified well-differentiated thyroid carcinoma or a follicular adenoma had preoperative Tc-99m or I-131 thyroid scintigrams showing a solitary reduced uptake and a Tl-201 scintigram showing uptake in the same lesion. This material was used to study the kinetics of Tl-201 in order to define the optimal separation (in terms of initial uptake and disappearance rate) between well-differentiated carcinomas and follicular adenomas.

This analysis was also enlarged with data from 24 patients from study III fulfilling the criteria for study IV. This pooled material comprised 41 follicular adenomas, 14 papillary and 2 follicular carcinomas.

Studies of NMR-relaxation-times of the thyroid in vitro (V).

During 1983, 14 specimens from six patients were investigated with NMR-measurements in vitro; two patients with a papillary carcinoma and four

patients with a benign lesion corresponding to a scintigraphically 'cold' area.

For each patient, samples were obtained from the suspected lesion and from macroscopically normal tissue. Four specimens contained cancerous tissue and ten showed normal tissue or benign lesions.

Prognostic factors of differentiated thyroid carcinomas (VI, VII)

During the period 1955-1972, 262 patients with histopathologically verified differentiated thyroid carcinomas were referred to the Department. Follow-up was concluded in May, 1981. The median follow-up time was 11 years. This material was used for analysis of factors of possible prognostic importance.

Excluded from further analysis were seven patients classified as having benign tumours, and 29 patients, whose microscopic slides could not be found for re-examination (VI:Table I). The excluded patients with malignant tumours did not differ from the entire group in respect to age, sex, or survival.

A total of 226 patients (86 per cent) thus form the basis for the following multivariate analyses:

-VI: Analysis A: Testing the validity and reproducibility of the EORTC prognostic index.

-VI: Analysis B: Analysis of pretherapeutic clinical factors.

-VI: Analysis C: Analysis of postsurgical (histopathological) tumour factors in combination with the patient factors of age at diagnosis and sex (221 patients).

-VII: The analyses were enlarged and carried out separately for papillary carcinomas (142 patients), follicular carcinomas (53 patients) and medullary carcinomas (26 patients).

METHODS

Scintigraphic techniques.

The radionuclides used were iodine-131 ($T_{1/2}=8$ d) in studies I-III, technetium-99m ($T_{1/2}=6$ h) in studies I-IV and thallium-201 ($T_{1/2}=73$ h) in studies III-IV.

Scanning was usually performed 24 hours after oral administration of 0.6 MBq iodine, 15-30 min after i.v. administration of 70 MBq technetium and 40-44 min after i.v. administration of 55 MBq thallium. Recordings were made with the patients in supine position and markers were applied over thyroid notch to provide exact localisation of the investigated nodule on the scintigram.

The iodine-scintigrams were performed according to the recommendations of the IAEA (Belcher et al. 1964) and digitalization and computer-assisted image-processing according to the method described by Möller et al. (1972). Technetium scintigrams were carried out with a gamma camera equipped with a pinhole collimator (ϕ 4 mm).

In studies III and IV, in which the diagnostic potential of thallium-201 was investigated, sequential 64x64 pixel images were recorded at 2 min intervals up to 40-44 min after the injection of thallium. Data were collected by a gamma camera equipped with a pinhole collimator (ϕ 4.7 mm) and a dedicated computer. In study III, the scintigraphically pathologic region was selected on the basis of a solitary defect in a previously performed iodine or technetium scintigram (III:Fig 3 a, b). A scintigraphically normal region (usually in the contralateral lobe) was chosen in the same way. The kinetics of thallium were evaluated by fitting single-exponential functions, $C \exp(-\lambda t)$ to area-normalized and background-subtracted count-density curves generated from the selected pathologic and normal regions (III:Fig 1).

A quotient of these exponentials from the pathologic and normal regions was calculated in order to minimize errors due to normal individual variation, variation in patient positioning, and calibration effects. The kinetics were evaluated in terms of relative uptake (C_p/C_n) and relative disappearance rate ($\lambda_p - \lambda_n$) (III:Table II).

In order to provide identical positioning for the thallium- and technetium-images, the method was further improved in study IV, where the images of the two radionuclides were recorded simultaneously in two channels (IV:Fig 1, 2). When using this double-isotope technique, data had to be corrected for channel cross-talk.

Clinical examination and staging.

The primary extent of the disease, as well as status during follow-up were routinely assessed by clinical examination including laryngoscopy, X-ray of the chest and axial skeleton, iodine-131-scintigraphy of the neck and a profile scan of the whole body.

The TNM-classifications used were those of AJCCS (1967) and UICC (1966) (Table III). Metastases, which were diagnosed within two months after primary diagnosis, were considered primary.

The time of follow-up was calculated from the day of decision for definite treatment.

Follow-up data were usually obtained during the first 10 years postoperatively from examinations at the Department and after that, usually from examinations at other hospitals in the region, or from questionnaires by mail.

A relapse was classified as local if it occurred in the thyroid bed, the residual thyroid tissue, the trachea, the oesophagus, or the midline neck in the operated area; as nodal metastases if it occurred in the ipsi- or contralateral cervical areas or in the upper mediastinum; and as distant metastasis if disease was proven outside the neck or the upper mediastinal area (Tables VI, VII).

Preoperative fine-needle aspiration cytology

Fine-needle aspiration cytology (AC) was routinely carried out on palpable 'cold' thyroid nodules investigated at the hospital. Most patients were aspirated by the cytopathologist, who afterwards also analysed the aspirate. AC was performed guided by the findings at scintigraphy. The needlings were carried out with a 22 gauge needle (outer diameter 0.6 mm) without local anaesthesia. The aspirates were stained with haematoxylin-eosin, but from 1973 onwards one or several air-dried slides were added for May-Grünwald-

TABLE III. A survey of commonly used T-classifications for malignant thyroid tumours.

	AJCCS 1967	AJCCS 1978	UICC 1966	UICC 1978
Tis	-	-	-	Pre-invasive carcinoma (carcinoma in situ)
T0	No palpable tumour	No available information on primary tumour	No palpable tumour	No evidence of primary tumour
T1	Tumour less than 5 cm in greatest dimension	Mobile tumour T1a Mobile tumour 4 cm or less in greatest dimension T1b Mobile tumour more than 4 cm in greatest dimension	Single tumour confined to the gland. No limitation of mobility or deformity of gland of scanning defect in gland normal to palpation	Single nodule in one lobe with or without deformity of the gland and with no limitation of mobility
T2	Tumour 5 cm or larger in greatest dimension	Partial fixation of tumour, any size, with or without neurologic involvement T2a Lateral position T2b Midline position	Multiple tumours or single tumour producing deformity of gland. No limitation of mobility	Multiple nodules in one lobe with or without deformity of the gland and with no limitation of mobility
T3	Tumour with direct extension into adjacent structures	Complete fixation of tumour, any size, with or without neurologic involvement; fistula	Tumour extending beyond the gland as indicated by fixation or infiltration of surrounding structures	Bilateral tumour with or without deformity of the gland and with no limitation of mobility or single nodule of the isthmus
T4	-	-	-	Tumour with extension beyond the gland capsule

AJCCS = The American Joint Committee on Cancer Staging. UICC = Union Internationale Contre le Cancer.

Giemsa staining (MGG). During the last years of study II MGG was almost exclusively used.

The primary cytodiagnoses were classified as malignant tumour, suspected malignant tumour, cellular atypia, indeterminate, benign tumour and not evaluable due to insufficient aspirate. Since 1975 the concept of indeterminate was used in the present material and covers sufficient aspirated material which could not be either classified as malignant or as benign. The cytodiagnoses of malignant tumour, as well as of suspected malignant tumour, were always considered positive for diagnosis of malignancy. All other cytodiagnoses were considered negative.

Histopathologic examination

All histologic specimens (except specimens included only in study II) were re-examined by one and the same pathologist. Re-examination was performed on the original slides, but if these were found to be of technically inferior quality, new slides were prepared from existing tissue blocks. The pathologist had no knowledge of the clinical course of each individual patient.

Histologic classification was made according to WHO (Hedinger and Sobin 1974). Medullary carcinomas, however, comprised only these carcinomas in which amyloid was seen. Since the presence of amyloid according to WHO is not a prerequisite for this diagnosis, a few medullary carcinomas may have been wrongly diagnosed as undifferentiated or follicular carcinomas.

The size and localization of the tumour (except small occult tumours) were estimated from the surgeon's operative-records and the histopathologic forms, but in some cases in studies II, VI and VII, the size was estimated from the slides of subsequent histopathologic examinations. The size of these tumours was corrected for a 25 per cent formalin-induced shrinkage (Åkerman, personal communication). Tumours equal to, or less than, 10 mm in their largest diameter were classified as occult carcinomas (UICC 1978), apart from study I, where the corresponding upper limit was 15 mm, according to Woolner et al. (1961).

Additional histopathologic characteristics evaluated in prognostic studies VI and VII were: tumour invasion beyond the thyroid capsule, marked cellular atypia, histopathologically verified lymph node metastases, and invasion

of vascular structures; further, but specifically for papillary carcinomas: ground glass phenomenon and psammoma bodies; and specifically for follicular carcinomas: Azkanazy cells (often called Hürthle cells) and the presence of tumour capsule.

In the study of NMR-relaxation-times (V), besides the histopathologic diagnosis, a visual quantitative histopathologic estimation was made of the proportions of colloid, fibrosis, necrosis, and hemorrhage in benign and cancerous tissue (V:Fig 1, V:Table I).

NMR-measurements

The NMR-measurements on human thyroid tissue in vitro were performed for protons at a frequency of 10.7 MHz with the pulse sequences (90° -t- 180° -t) and for T1 and T2, respectively. The measurements were done at 37° C on fresh samples weighting 0.5-3.2 g.

The T1- and T2-values were correlated to quantitative histopathologic tissue characterization, and in most cases also to total water content.

Statistical methods

Survival was estimated according to the life table technique (Cutler and Ederer 1958). When analysing differences in cumulative survival between groups, the Lee-Desu test was applied (Lee and Desu 1972).

Prognostic factors were assessed multivariately by Cox's proportional hazard model (Kalbfleish and Prentice 1980).

Bivariate correlation between covariates was evaluated by Pearson's correlation coefficient.

All p-values were two-tailed, and values less than 5 per cent were considered significant.

Comparisons were made with national life table figures representative for a Swedish population with the same age- and sex-distributions as the investigated group of patients, in order to estimate death in intercurrent disease (Ederer et al. 1961).

Treatments

The different treatment modalities employed (ie. surgery, radiotherapy, radioactive iodine therapy, or a combination of these) for the patients included in the prognostic studies VI and VII are presented in Table IV. Most of these patients (n=204) have also received thyroid hormone medication, but only three patients have been treated with additional chemotherapy.

When investigating the different treatment modalities in regard to time it was found that surgery became more frequent during the years, but there was also a tendency to less advanced operations; radiotherapy became less frequent; and radioactive iodine therapy remained unchanged.

Therapy has not been taken into consideration in the analysis of survival because of the complexity and the continual change of the treatment policy.

TABLE IV. Type of therapy in 226 patients with differentiated thyroid carcinomas (VI, VII).

Histology	Surgery	Rx	Surgery + Rx	I-131	Surgery + I-131	I-131 + Rx	Surgery + I-131 + Rx
Papillary carcinoma	53	4	33	1	31	1	20
Follicular carcinoma	6	-	11	7	25	1	7
Medullary carcinoma	13	1	6	-	3	-	3
Total	72	5	50	8	59	2	30

Rx = Radiotherapy. I-131 = Radioactive iodine therapy

RESULTS

Preoperative scintigraphy with iodine-131 and/or technetium-99m (I)

An evaluation of preoperative scintigrams, based on a material of 83 consecutive histopathologically confirmed thyroid carcinomas was carried out with respect to:

Scintigraphic appearance: A solitary reduced uptake on the scintigram was found in approximately 65-70 per cent of the total material as well as of the well-differentiated thyroid carcinomas (I:Table I). The scintigraphic image of undifferentiated carcinomas was mostly a solitary reduced uptake often in the form of a total disappearance of the affected lobe.

Scintigraphic detectability: The minimum detectable size was 10 mm for papillary and follicular carcinomas, whereas in the screening group of hereditary medullary carcinomas, several scintigrams were judged as normal although a tumour measuring 10-15 mm in diameter was found at subsequent operation in these cases (I:Fig 1).

The value of additional computer-assisted image processing: By these investigations, performed in 45 patients, multinodular lesions were more distinctly visualized (I:Table IV, I:Fig 2). However, this method did not change the interpretation of the dot scintigram in any case.

Scintigraphy and preoperative fine-needle aspiration cytology (AC): The AC-diagnosis gave a false benign diagnosis in 22 of 73 patients (30 per cent) (I:Table II). Most of these tumours were rather small (<15 mm). In eleven cases, the tumour was not hit at the needling (I:Table III). In seven of these patients, however, the scintigram showed either an irregular uptake or a normal image, and consequently the scintigram was not a guide for the cytologist. The computer-processed scintigrams were usually not available at the needling.

Preoperative fine-needle aspiration cytology (II)

An evaluation of preoperative fine-needle aspiration cytology (AC), based on a material of 203 consecutive histopathologically confirmed thyroid carcinomas was carried out with respect to:

Cytodiagnosis (II:Table I): A cytologic finding of a malignant tumour or suspicions of a malignant tumour were found in 56.7 per cent (n=115) of the

patients. Cellular atypia and indeterminate cytodiagnosis accounted for 11.8 per cent (n=24) and false benign for 27.6 per cent (n=56) of the material. In 3.9 per cent of the cytodiagnoses were not considered evaluable, as the aspirate did not contain a sufficient number of cells to be classified.

Sensitivity of AC (II:Table II): If only cytodiagnoses of malignancy or suspicions of malignancy were considered as positive, the sensitivity of AC for the total material was 0.57. The sensitivity for diagnosing a medullary, or an undifferentiated carcinoma was much better (0.82 and 0.84, respectively). If the diagnosis of cellular atypia or indeterminate at AC also were considered as positive findings the sensitivity for diagnosing a papillary carcinoma or a follicular carcinoma would increase (0.49 to 0.63 and 0.42 to 0.67, respectively).

Causes of a false benign AC (II:Table III): The most common cause of a false benign AC was an aspiration miss, but quite half of these tumours not hit at needling were of occult type. A microscopic misinterpretation was the second most usual cause. Papillary and follicular carcinomas accounted for all of these cases (apart from one case of malignant lymphoma).

Cytologic diagnosis of cellular atypia and indeterminate: The histologic diagnosis was in all of these cases a papillary (n=18) or a follicular carcinoma (n=6). In six of the papillary carcinomas the aspiration was not performed against the carcinoma (three of them being occult), but against palpable tumours, which proved to be follicular adenomas. The other carcinomas with these cytodiagnoses were microscopically misdiagnosed.

An evaluation of AC, based on 217 consecutive histopathologically confirmed benign thyroid disorders, was carried out with respect to specificity of AC (II:Table IV). In only 1.8 per cent (n=4) did cytology indicate a malignancy or suspicion of a malignant tumour. The specificity of AC for confirming a benign mass was thus 0.98. If, however, cytologic diagnoses of cellular atypia or indeterminate findings were also considered as positive findings, the specificity of the method would decrease to 0.86.

Scintigraphy and dynamic studies with thallium-201 (III, IV)

Image-interpretation of thallium scintigraphy was performed in 46 patients with later histologically verified malignant or benign disorder (III:Table II). In 36 of these patients, it was also possible to evaluate dynamic studies.

At image interpretation, ten of eleven differentiated thyroid carcinomas (7 papillary, 2 follicular and 2 medullary carcinomas) showed a thallium-uptake increased or equal to that of normal thyroid regions. There was no histologic explanation (eg. hematoma or cystic degeneration) for the decreased uptake in one papillary carcinoma.

On the other hand, follicular adenomas, particularly those mainly composed of microfollicular and Azkanazy cells, also usually showed an increased or equal uptake. Follicular adenomas with decreased uptake were either cystic, saturated with colloid, or showed signs of bleeding. Cystic lesions never showed an accumulation of thallium.

Cervical lymph node metastases could be seen in three out of five patients with later histologically verified metastases. The two cases with no uptake were cystic.

TABLE V. Initial uptake and disappearance rate of thallium-201 in different histologic lesions (Mean $\pm$ SD).

Histology	No. of patients	Rate constant $\lambda_p \text{ min}^{-1}$	Relative disappearance rate $\frac{(\lambda_p - \lambda_n)}{\lambda_p} \text{ min}^{-1}$	No. of patients*	$e^{\text{Log uptake ratio}} \ln \left(\frac{C_p}{C_n} \right)$
Carcinoma	7	0.015 $\pm$ 0.007	-0.017 $\pm$ 0.015	5	0.240 $\pm$ 0.43
Follicular adenoma	22	0.023 $\pm$ 0.010	-0.005 $\pm$ 0.011	16	0.032 $\pm$ 0.45
Nodular goitre	7	0.025 $\pm$ 0.008	0.000 $\pm$ 0.005	4	-0.061 $\pm$ 0.44

*Grossly asymmetrical glands excluded.

Analysis of dynamic data from 36 consecutive patients, with a 'cold' lesion on the technetium- or iodine-scintigram, is presented in Table V. The raw data (λ_p) take the form of overlapping, roughly Gaussian distributions, with mean and standard deviation as shown. The normal tissue showed no correlation to the diagnoses of the pathologic tissue in the same patient. The rate constant for the normal tissue in the contralateral lobes (λ_n) was $0.028 \pm 0.009 \text{ min}^{-1}$. The rate constants for cancer and adenoma were statistically separated from the normal rate at the 5 per cent-level. The separation was enhanced by the relative disappearance rate ($\lambda_p - \lambda_n$). The uptake ratios were difficult to evaluate, because of unknown lobe thickness.

There was a tendency to higher relative uptake in the cancer group, when a conservative selection was made by excluding glands where the pathologic lobe had an area twice as large, or more, than that of the normal lobe.

Further investigations were performed (IV) in order to define conditions in terms of initial thallium uptake ratio and the relative disappearance rate for optimal separation between well-differentiated carcinomas and follicular adenomas. The patients included (9 papillary carcinomas and 24 follicular adenomas) are presented in IV:Fig 4. This figure shows that the carcinomas are located in the left half of the diagram, indicating low disappearance rates, whereas there was no clear separation in initial uptake between carcinomas and follicular adenomas. A significant difference could thus only be demonstrated ($p<0.01$) between the mean values of disappearance rate for the two groups.

These measurements have been pooled with corresponding data from patients included in study III, who also fulfilled the criteria of study IV. These pooled data are presented in Fig 3.

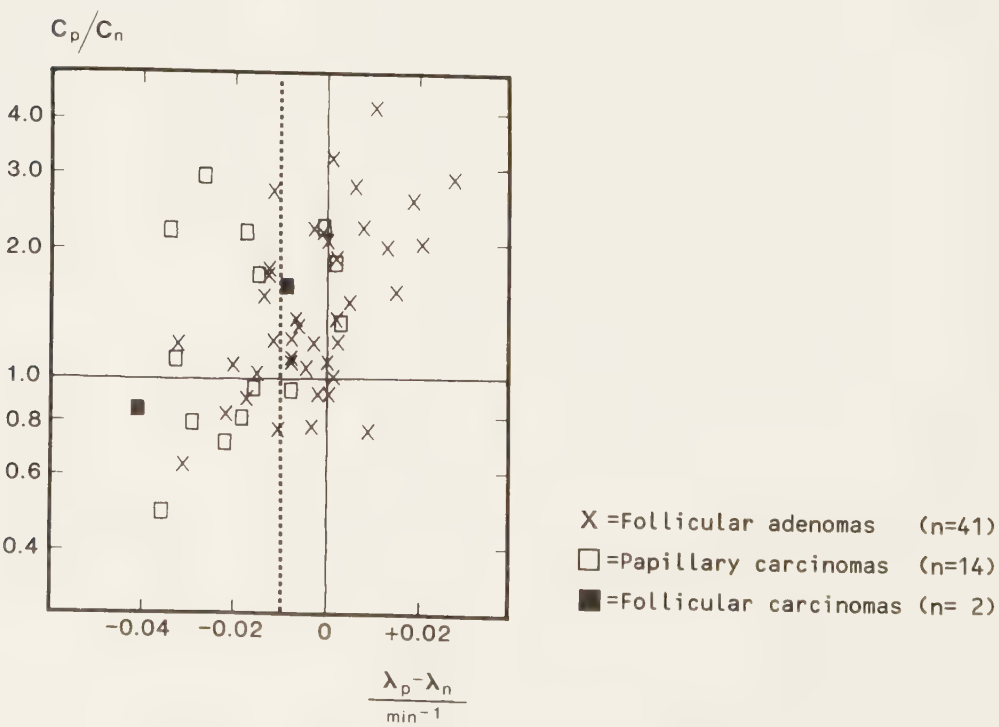


Figure 3. Extrapolated zero-time uptake ratio $\ln(C_p/C_n)$ vs. relative disappearance rate in 57 patients.

Discriminant analysis (Van de Geer 1971) of this material showed a significant difference in the disappearance rate ($p=0.0001$), but not in initial uptake ($n=0.45$). No interaction was shown between the two rates ($p=0.86$). The optimal value for discrimination was found to be at a disappearance rate of -0.01 min^{-1} . From the clinical point of view, this value divides the patients in a high-risk group (11/23 patients with carcinomas) and a low-risk group (5/34 patients with carcinomas).

Studies of NMR-relaxation-times in vitro (V).

The T1- and T2-values of malignant and benign tissues ranged between 419-721 ms and 47-96 ms, respectively. Both the T1- and T2-values varied in direct proportion to the total water content, but they showed a tendency to be inversely proportional to the amount of colloid (V:Fig 3).

Fibrosis

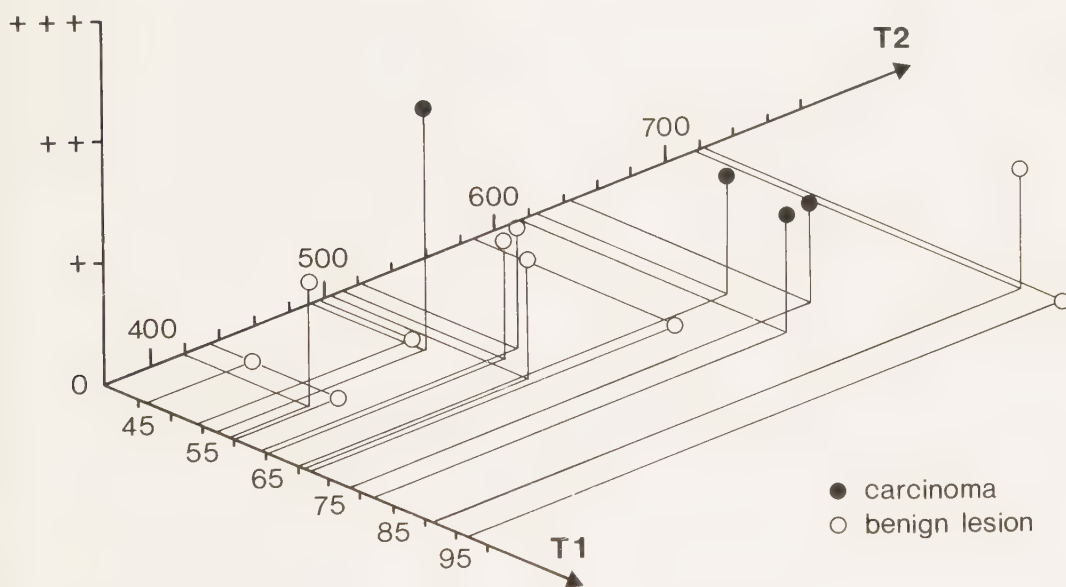


Figure 4. T1- and T2 values in relation to proportion of fibrous tissue in carcinomas and benign lesions.

Figure 4 illustrates the relations between the three parameters T1- and T2-values and the degree of fibrosis in the 14 investigated specimens. Three out of four specimens with papillary carcinomas (●) had a narrow range of T1- as well as of T2-values. These tumours showed the same proportion of fibrosis and colloid. One sample containing papillary carcinoma had shorter

T1- and T2-values, but showed a greater proportion of fibrous tissue, compared to all of the other specimens investigated.

T1- and T2-values thus seem to reflect differences in tissue composition, but further investigations are needed before any evaluation can be done on their usefulness for discriminating malignant from benign lesions.

Prognostic factors of differentiated thyroid carcinomas (VI, VII)

Various possible prognostic factors of differentiated thyroid carcinomas were evaluated, both for the total material (VI), as well as separately for each histologic group (VII). The outcome of these patients mainly based on clinical investigations are reviewed in Table VI and VII. Deaths in intercurrent disease were estimated by comparison with an age and sex adjusted population.

1. Testing the reproducibility and validity of the EORTC-prognostic index (VI:Analysis A): Neither age nor sex proved to be important predictors. Only two parameters could be reproduced as significant: locally clinically advanced disease and distant metastases.
2. Analysis of pretreatment factors (VI:Analysis B): The TNM-variables were found to be the only important predictors. In this analysis only, lymph node metastases were found to be of prognostic importance.
3. Analysis of postsurgical factors (VI:Analysis C): In this analysis marked cellular atypia and tumour invasion beyond the thyroid capsule were found to be important prognostic factors.
4. Analysis of prognostic factors by histologic group (VII): The important predictors for papillary carcinomas (n=142) were: tumour invasion beyond thyroid capsule and marked cellular atypia; for follicular carcinomas (n=53): tumour invasion beyond the thyroid capsule, marked cellular atypia and distant metastases; and for medullary carcinomas (n=26): only tumour invasion beyond the thyroid capsule.

(Distant metastases were, however, not evaluated for analysis C in study VI and for papillary and medullary carcinomas in study VII, due to the small number of patients with this variable).

TABLE VI. The outcome of 226 patients with differentiated thyroid carcinomas by histology (VI, VII).

Histology	No. of patients	Persistent tumour	Local recurrence	Cervical lymph node metastases	Distant metastases	Death from ca.thyroid	Total number of deaths
Papillary carcinoma	143	7 (4.9 %)	6 (4.2 %)	10 (7.0 %)	15 (10.5 %)	15 (10.5 %)	38 (26.5 %)
Follicular carcinoma	57	6 (10.5 %)	3 (5.3 %)	6 (10.5 %)	15 (26.4 %)	14 (24.6 %)	25 (43.9 %)
Medullary carcinoma	26	6 (23.1 %)	-	3 (11.5 %)	6 (23.1 %)	5 (19.2 %)	10 (38.5 %)
Total	226	19 (8.4 %)	9 (4.0 %)	19 (8.4 %)	36 (15.9 %)	34 (15.0 %)	73 (32.0 %)

TABLE VII. Analysis of fatal cases with differentiated thyroid carcinomas by histologic type (VI, VII).

Histology	No. of patients	Persistent tumour	Local recurrence	Lymph node metastases	Distant metastases	Metastatic site Lung Bone
Papillary carcinoma	15	6	4	4	10	7 3
Follicular carcinoma	14	5	3	3	11	9 3
Medullary carcinoma	5	4	-	3	5	3 2
Total	34	14	7	10	26	19 8

GENERAL DISCUSSION

Preoperative diagnosis

The finding of a solitary palpable nodule in the thyroid gland of a patient at clinical examination often arouses the suspicion of malignancy. Such a finding is not uncommon; one American study indicates that 2.8 per cent of individuals between 30 and 59 years of age have a solitary nodule at clinical examination (Vander et al. 1968), while the corresponding figure for women aged 48 to 53 living in Malmö, was 6.5 per cent (Borup Christensen et al. 1984).

When clinical factors, such as age, sex and palpation findings (firmness of the nodule), are taken into account the probability of making correct diagnosis of the nature of the nodule will increase (Hoffman et al. 1972, Psarras et al. 1972, Borup Christensen, In press), but these clinical criteria are not specific enough to permit a reliable distinction between benign and malignant lesions. Regression of a suspected nodule with thyroid suppressive therapy will not give additional information for a differential diagnosis nor permit a reliable distinction (Aschcraft and van Herle 1981), and furthermore, elderly patients may not be able to tolerate the dosages of thyroid hormone required to achieve suppression (Clark and Demling 1976).

Scintigraphic imaging of a thyroid nodule with iodine-131 or technetium-99^m may make a diagnosis of carcinoma highly improbable if the scintigram shows an accumulation of the radionuclide or an autonomously functioning nodule. Technetium-99^m may, however, in rare cases fail to show a cold area that would have been detected by iodine-131 (Alderson et al. 1976, Erjavec et al. 1977).

The risk of malignancy in the solitary palpable nodule will decrease markedly (to approximately 5 per cent) if the scintigram reveals that the nodule is part of a multinodular goitre (Dische 1964, Alderson et al. 1976), unless representing a dominant non-functioning lesion. In such a case it should be treated as a solitary 'cold' nodule (Alderson et al. 1976). By these findings conventional scintigraphy have reduced the number of patients in whom further investigation is needed without much loss of sensitivity. Fine-needle aspiration cytology should be performed after scintigraphy, because the scintigram should be a guide at needling, and also to avoid a 'needle-induced hematoma', which could present itself as a cold area at imaging. If the cytologic examination reveals a carcinoma, surgery is strongly indicated, since falsely positive cytology is rare (II, Löwhagen et al. 1979).

After scintigraphy, a cystic tumour should be drained and any remaining palpable nodule should be needled. Problems in diagnosing cystic carcinomas occurred in the present study (I, II) as well as in other studies (Suen and Quenville 1983).

Ultrasound may be helpful in distinguishing cystic from solid lesions, but cannot show whether the lesion is malignant or not (Chilcote 1976). If the lesion is larger than 40 mm in diameter, this method often gives inconclusive results because of necrosis and hemorrhage that often occur in large tumours (Blum et al. 1972).

The major diagnostic problem is the palpable firm and scintigraphically 'cold' nodule, where cytology is negative or inconclusive (I-V), because the risk of malignancy in such a nodule is reported to be of the order of 20 per cent (Dische et al. 1964, Kendall and Condon 1969, Alderson et al. 1976, Burrow et al. 1978). These data are, however, often based on small and selected patient materials, and can vary between 3 and 43 per cent (Shimaoka and Sokal 1964). When evaluating these risk figures, it must, furthermore be taken into consideration that the prevalence of occult papillary carcinoma is relatively high in investigated European and American populations. Figures, based on large series of consecutive autopsies, range between 5 and 9 per cent (Sampson et al. 1974, Bondeson and Ljungberg 1981). Even, if a correction is made for the number of occult carcinomas found at operation there is an increased frequency of carcinomas in solitary 'cold' nodules. To eliminate the selection bias, and to evaluate how often a carcinoma presents itself as a solitary 'cold' nodule, the findings in the preoperative scintigraphy of 83 consecutive histopathologically confirmed thyroid carcinomas have been analysed (I). This type of image was found in 70 per cent of the entire group (65 per cent of well-differentiated carcinomas), which supports the statement that a solitary 'cold' nodule is the most frequent presentation of a thyroid carcinoma. The minimum scintigraphically detectable size of thyroid carcinomas was found to be in the order of 10 mm, with the exception of 'screened' hereditary medullary carcinomas where larger tumours were missed at scintigraphy (I). The diminished detectability of medullary carcinomas has also been reported by Rasmussen (1982). The scintigraphic examinations in study I were, however, mostly performed with rectilinear scanners and iodine-131. It is possible to detect lesions in the thyroid gland as small as 5 mm, under optimal conditions with technetium-99m-per-

technetate and a gamma camera equipped with a pin-hole collimator (Ryo et al. 1976).

The clinical problem of diagnosing thyroid carcinoma will not be solved by increasing the scintigraphic sensitivity (=detecting more occult carcinomas) but by increasing the scintigraphic specificity (=excluding more lesions suspected for carcinomas). In order to increase the scintigraphic specificity, especially of the 'cold' nodule, several other radionuclides and radiopharmaceuticals have been used with varying degrees of success, e.g. cesium-131 (Charkes et al. 1965, Murray et al. 1970), and selenium-75-methionine (Weinstein et al. 1971). The low energy of cesium-131, and the poor signal-to-noise ratio, may explain most of the negative results reported (Murray et al. 1970). Some radionuclides, have, however, been shown to be more specific for certain types of thyroid carcinomas, such as gallium-67-citrate for anaplastic carcinomas (Kaplan et al. 1974, Higashi et al. 1981, Senga et al. 1982), and thallium-201-chloride for differentiated carcinomas (III, Senga et al. 1982)

Differing results are reported from thallium scintigraphy in medullary carcinomas (III, Parathasarathy et al. 1980, Senga et al. 1982, Ochi et al. 1982).

The diagnosis of medullary and undifferentiated carcinomas is, however, easier than the diagnosis of well-differentiated carcinomas, reflected by the cytologic sensitivity in these tumours is high (II). In addition, for diagnosing occult medullary carcinomas the biochemical tests have a superior sensitivity (Telenius-Berg et al. 1977, Wells et al. 1978) and for undifferentiated carcinomas, the medical history, clinical examination and the conventional scintigraphic image mostly give sufficient information (I, Tennvall et al. 1979).

The sensitivity of AC for demonstrating well-differentiated thyroid carcinomas was found to be low, even if occult tumours were excluded (II). Several of the AC from these lesions, despite a representative aspirate, were either cytologically misinterpreted as benign tumours or were classified as cellular atypia or indeterminate (II). The cytologic findings of these last two categories do not, however, give any guidelines for the physicians. It is therefore important to clarify in what way cellular atypia and indeterminate cytodiagnoses are included in the results of AC (II, Block et al. 1983).

Serum thyroglobulin as a preoperative tumour marker for papillary and follicular carcinomas has, however, shown a poor sensitivity (van Herle et al. 1975), but considerably elevated values in euthyroid patients support a malignant diagnosis (Borup Christensen, In press).

The sensitivity of thallium scintigraphy appears to be of the order of 90-95 per cent, while the specificity was inadequate (36-54 per cent) for distinguishing between benign lesions and carcinomas (Hisada et al. 1978, Tonami et al. 1978, Tennvall et al. 1982). In study III, as in a more recent report by Palermo et al. (1982), it was found that carcinoma as a group might have a slightly decreased disappearance rate of thallium, compared to adenomas. The kinetic analysis might thus increase the specificity of thallium investigations. This has also been confirmed by performing delayed thallium scintigraphy (3-5 hours after i.v. administration) (Ochi et al. 1982).

A further evaluation of the kinetics of thallium was performed in study IV, in order to define conditions for optimal separation between well-differentiated carcinomas and adenomas. It was found that adenomas could be significantly separated from carcinomas by the elimination, but not by the initial uptake. Table VIII shows a comparison between cytologic diagnosis and thallium elimination in 14 patients with histologically confirmed well-differentiated thyroid carcinomas (based on a comparison of the results of studies II, III and IV).

TABLE VIII. Comparison between cytologic findings and thallium elimination in 12 papillary and 2 follicular carcinomas. A delayed disappearance rate ($< -0.01 \text{ min}^{-1}$) is regarded as strongly suspected for carcinoma (Compare with Fig 3). No occult carcinomas are included.

Cytodiagnosis	Thallium-elimination	
	+	-
Malignant tumour	5	3
Suspect for malignant tumour	1	-
Cellular atypia	2	1
Benign tumour	2	0

Measurements of the total iodine content of thyroid nodules by quantitative americium-241 fluorescent scanning have demonstrated that most malignancies contain no detectable stable iodine, whereas at least 50 per cent of benign nodules contain higher levels (Patton et al. 1976). This method might also improve the preoperative diagnosis of well-differentiated thyroid carcinomas. Computerized morphometric measurements of aspirates from follicular neoplasms (Boon et al. 1982) may be a possible approach in distinguishing follicular carcinomas from adenomas.

The NMR-technique might open new possibilities for the differential diagnosis of thyroid nodules, since in vivo NMR-images not only yield anatomical information, but also physiologic and chemical characteristics of tissues. The relaxation times (T1- and T2-values), the proton density and the blood flow are the determinants of contrast in proton nuclear magnetic images (Fullerton 1982). Measurements of the proton NMR-relaxation-times performed on thyroid samples seem to reflect differences in tissue composition (V, de Certains et al. 1982). Further investigations are needed, however, and possible circulation-induced effects must be taken into account before the value of in vivo proton NMR-imaging can be assessed in discriminating thyroid carcinomas from benign lesions. A possible alternative in the future can be in vivo NMR-spectroscopy, performed at higher magnetic field strengths for measuring nuclei other than protons, eg. phosphorus-31.

Prognostic factors

Numerous factors have been asserted to be important predictors of survival for thyroid carcinomas, especially for differentiated thyroid carcinomas (Cady et al. 1976, 1979, Proye et al. 1981, Tscholl-Ducommun and Hedinger 1982). The two major reasons for the contradictory results of different prognostic studies are measuring confounding factors, instead of the factors of real importance for survival, and the selection bias of the investigated patient material. By using multivariate analysis, it is possible to control these confounding factors. Apart from the present study, there have hitherto only been two reports on prognostic factors for thyroid carcinomas, in which this method has been employed (Byar et al. 1979, Warnebo et al. 1981). In these reports, however, the effects of death in intercurrent disease have not been taken into consideration. As age at diagnosis not only contains prognostic information relevant for the tumour, but also for intercurrent disease, there is always a risk of overestimating the importance of age, especially when the malignant disease

has a protracted course. It is therefore necessary to analyse the role of these 'age-correlated' tumourfactors (VI, VII). Furthermore in the multivariate analysis by Warnebo et al. (1981) but also in several mono- or bifactorial analyses (Cady et al. 1976, 1979) age at diagnosis has been evaluated as a categorical variable in contrast to the estimation of age as a continuous variable as in the present study and in the study of the EORTC group (Byar et al. 1979).

In the present material the number of autopsies is small (20 per cent). The causes of death, furthermore, found in hospital records and/or death certificates, is frequently incomplete or inaccurate. Moreover, apart from the question of the validity of this information, it is often difficult to interpret known facts. Even if an autopsy is performed, it is sometimes impossible to determine whether the patient died from cancer or from intercurrent disease with persistent cancer (Berkson and Gage 1952).

It is, however, not possible to use the relative survival in a semiparametric multivariate model, such as the Cox's model, but on the other hand this model is robust and insensitive to outliers in survival (Byar 1982).

It is not advisable to use the same model on different tumours with great divergency in biologic behavior as in the EORTC-study (Byar et al. 1979), since the same variable might have different prognostic significance (VII).

Only a few studies have included all thyroid carcinomas registered in a demographically well-defined population (Franssila 1975, Lindahl 1975, Borup Christensen et al. In press). This is the only way to avoid selection bias. To estimate the magnitude of selection bias in the present study the annual referral rates from the catchment area of the Department was investigated. Comparison was also made between the sex ratio, the proportion of well-differentiated thyroid carcinomas and the mean age of referred patients, and all reported cases of cancer of the thyroid in the same population. These aspects showed the referred material to be representative for the reported cases in the population.

Differences in survival rates may be attributed to the differences in the geographical distribution of the different histologic types of thyroid carcinoma (Cuello et al. 1969, Hakulinen et al. 1983). Papillary carcinoma

is the predominant type in coastal areas (Williams et al. 1977) whereas follicular and anaplastic carcinomas are more frequently found in areas with endemic goitres (Bubenhof and Hedinger 1977). Iodization of salt in the endemic goitre areas can change the histologic distribution of thyroid carcinoma in the population (Bubenhof and Hedinger 1977).

In material originating from goitrous areas, the proportion of extrathyroidal tumour growth is high, probably as a consequence of late detection in the goitrous gland. According to reports regarding papillary carcinomas from Bavaria and Austria (Löhrs et al. 1983, Krisch et al. 1980), 45 per cent and 37 per cent, respectively, were found to have extrathyroidal disease. The corresponding figure from Finland was 43 per cent (Franssila 1978). In contrast, extrathyroidal papillary carcinoma was found in only 7-15 per cent according to American reports (Mazzaferri and Young 1981, Woolner et al. 1961, Cady et al. 1976). These figures are, however, probably not only due to geographical differences.

These differences might also be explained by the accumulation of less advanced (Mazzaferri and Young 1981) or more advanced tumours, or cases with particular tumour-types, in certain centres (Staunton and Skeet 1979). In the present study, there is an accumulation of hereditary medullary carcinomas. Since the report on papillary carcinomas by Mazzaferri and Young was based on patients under the care of US Air Force physicians, the young mean age at diagnosis (32 years) as well as the great proportion of men (women/men 1.6:1) is probably only an expression of selection bias. In prognostic reports based on surgical series many inoperable cases and patients with distant metastases have been excluded (Woolner et al. 1961, 1971, Hirabayashi and Lindsay 1961, Lacour et al. 1969, Cady et al. 1976, 1979). On the other hand there might be an accumulation of more advanced tumours in reports from oncologic departments, even in the present report. The continuous changings of T-classifications (Table III) have also made comparisons more difficult.

The proportion of detected cases may also vary with time, due to changing indications for surgery. A great time-variation in the number well-differentiated carcinomas can be observed in the material of Cady et al. (1976), where half the number of patients were diagnosed during the third decade of an investigation period of forty years. In the present material, no such fluctuations with time were found (Fig 1). The high ratio of papillary

carcinomas incidently found at operation in the American reports (Frauenhofer et al. 1979) might reflect liberal indications for operating thyroid nodules. The proportion of detected small tumours would in this way probably increase among the young and the middle-aged, because elderly patients are less likely to be submitted to surgery, particularly in cases of small thyroid nodules.

Histopathologic considerations

Despite the commonly used WHO-classification (Hedinger and Sobin 1974), Saxén et al. (1978) have demonstrated a great observer variation in the histologic classification of thyroid carcinomas (especially of follicular carcinomas) and they consequently stress the importance of having all cases reviewed by the same pathologist, in order to obtain reliable results for comparative studies. In the present study, all of the histologic slides included in the prognostic reports (VI, VII) have been reviewed by the same pathologist. In the study by Woolner et al. (1961), however, encapsulated follicular tumours that displayed marked cellular atypia, but without evidence of invasion have been classified as follicular carcinomas. These cases were included because such lesions have earlier reportedly metastasized, but the probable explanation for this is that these diagnostic criteria were not present in the slides used for microscopic examination. By a great number of sections and careful examination the proportion of slightly invasive follicular carcinoma (Ito et al. 1980) and occult papillary carcinoma (Bondesson and Ljungberg 1981) would increase. Marked cellular atypia consequently, is not a diagnostic criterion for follicular carcinoma, but according to the present study (VI, VII), an important prognostic factor when histology reveals evidence of tumour invasion.

CONCLUDING REMARKS

Scintigraphy (Iodine-131 or technetium-99m): A solitary reduced uptake was the most common appearance in preoperative scintigrams (70 per cent) of a consecutive series of patients with confirmed thyroid carcinomas. The minimum detectable size in the scintigrams (apart from scintigrams with irregular uptake) was 10 mm for papillary, follicular and undifferentiated thyroid carcinomas. The scintigrams of the medullary carcinomas, however, especially in the group of the hereditary type, were in several cases considered normal despite the presence of tumours measuring 10 to 15 mm. Multifocal areas in the scintigram, representing tumours were often missed at fine needle aspiration. Computer-processed scintigrams were superior in showing multifocal tumours, but this did not in any case change the interpretation of the original scintigram.

Aspiration cytology: Since a false positive cytology of thyroid was rare all tumours with a cytologic finding indicating a malignancy or suspicion of malignancy should be subject to further measures. However, only half of all malignant thyroid tumours could be diagnosed with cytology. The most common cause of a false benign cytology was an aspiration miss. About half of these 'missed' tumours were, however, of the occult type. A microscopic misinterpretation was the second most usual cause of a false benign cytology. Papillary and follicular carcinomas accounted for all these cases (apart from one case with malignant lymphoma). In addition the aspiration cytology of papillary and follicular carcinoma was, despite good quality of the cytologic aspirate, not seldom indeterminate or showed signs of cellular atypia only.

The major diagnostic problem is thus, the scintigraphically 'cold' nodule, where cytology gives a negative or an inconclusive diagnosis. In these cases, there is a need of complementary investigations.

Thallium scintigraphy: A cold (iodine or technetium) thyroid nodule, corresponding to a visually decreased thallium uptake is most likely a benign disorder, but a visually increased thallium uptake might represent a well-differentiated thyroid carcinoma as well as a follicular adenoma. Adenomas could, however, be significantly separated from carcinomas by the elimination rate ($p=0.0001$), but not by the initial uptake. From a clinical point of view, it was possible to categorize the patients in a high-risk group (11/23 patients with carcinomas) and a low risk group (5/34 patients with carcinomas).

Future diagnostic possibilities: Since the NMR-technique provides anatomical information, as well as information of physiologic and chemical characteristics, it might be a progress in the diagnosis of thyroid nodules. The T1- and T2-values are important determinants of contrast in the NMR-image. The present study demonstrates that these values from in vitro measurements of thyroid samples reflect different tissue compositions.

Prognostic factors: Clinical assessment (VI) as well as preoperative aspiration cytology give guidelines for prognosis, but different histopathologic criteria provide more precise prognostic information in the individual case. According to multivariate analysis, and when deaths in intercurrent disease were estimated, neither age at diagnosis nor sex were found to be important predictors of survival in papillary, follicular or medullary thyroid carcinomas.

The EORTC-prognostic index (Byar et al. 1979) thus, could not be reproduced on this material consisting of differentiated thyroid carcinomas with a long follow-up.

For the different histologic groups, the following predictors were identified:

Papillary carcinomas: tumour extension beyond the thyroid capsule and marked cellular atypia.

Follicular carcinomas: tumour extension beyond the thyroid capsule, marked cellular atypia and distant metastases.

Medullary carcinomas: tumour extension beyond the thyroid capsule.

(Distant metastases at diagnosis could not be evaluated for papillary and medullary carcinomas due to the small number of patients with this characteristic).

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PREOPERATIVE SCINTIGRAPHY WITH CORRELATION TO CYTOLOGY AND HISTOPATHOLOGY IN CARCINOMA OF THE THYROID

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Scintigraphy and aspiration cytology have since long been considered to be a useful combination in the diagnosis of thyroid disease (EINHORN & FRANZÉN 1962). However, recently SAXE (1979) and ESSELSTYN (1981) raised doubt of the value of thyroid-imaging in the preoperative diagnosis of thyroid carcinoma.

Conventional thyroid scintigraphy with radioiodine or $^{99}\text{Tc}^{\text{m}}$ is the only routine imaging procedure, besides being simple and cheap, that yields information if a palpable nodule is solitary and 'cold', or if it is a part of a multinodular goitre. This observation is important due to the higher risk of malignancy in a solitary cold nodule. On the other hand, it is not reported how often a carcinoma presents itself as a 'cold' nodule, and if there are differences in the scintigraphic appearance for different histologic types.

The purpose of the present investigation, based on consecutive histologically confirmed thyroid carcinomas, was therefore to correlate the different histologic types to the scintigraphic image and to assess their scintigraphic detectability. The results of preoperative aspiration cytology were also correlated to these parameters and the value of computer processing of scintigraphic images was evaluated.

Material and Methods

During the period 1969 to 1975 a total of 167 patients with different types of thyroid carcinomas were referred to or diagnosed at the Department of

Oncology. The annual incidence of thyroid carcinomas in the region served by the hospital was 35 to 40 cases (Cancer Incidence in Sweden, 1973). The criteria for inclusion in the present investigation were the presence of a thyroid scintigram preoperatively and a histologic confirmation at total thyroidectomy or lobectomy (except in 8 patients with undifferentiated carcinomas of large cell types where the diagnosis was established by an open biopsy). A total of 83 patients (50%) fulfilled these criteria and form the basis for the present analysis; 28 were men and 55 women. The median age was 55 years (range 14–84).

The patients included in the present investigation did not differ from the entire patient group with respect to age, sex, or the distribution of different histologic types. The only exception was medullary carcinomas, which were slightly overrepresented.

In 78 of the patients thyroid scintigraphy was carried out with ^{131}I as the imaging agent. In 14 patients scintigraphy was performed using $^{99}\text{Tc}^{\text{m}}$ pertechnetate; thus 9 patients had a thyroid scan carried out by both methods, while 5 patients were examined with $^{99}\text{Tc}^{\text{m}}$ only.

The thyroid examinations were performed after oral administration of usually 0.6 MBq (approx. 16 μCi) ^{131}I . Recordings were made with the patients in supine position and markers were placed over the thyroid notch and the suprasternal notch. The distance between them was used as a reference for the

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Table 1
Scintigraphic appearance and histopathologic diagnosis in 83 patients

Histopathology of the tumours	Solitary reduced uptake		Irregular uptake	Normal uptake	No.
	Unilaterally	Bilaterally			
Differentiated (n=54)					
Follicular	4	—	2	—	6
Papillary	17	2	6	3	28
Mixed	9	3	7	1	20
Medullary (n=16)					
Sporadic with symptoms	3	1	1	—	5
Hereditary with symptoms	2	2	—	—	4
Hereditary without symptoms	4	—	—	3	7
Undifferentiated (n=13)					
Giant and spindle cell	3	—	—	—	3
Small anaplastic	1	—	—	—	1
Lymphoma	1	—	1	—	2
Unclassifiable	6	—	1	—	7
Total	50	8	18	7	83

determination of the size and localization of the lesions.

Uptake measurements after 2 hours and 24 hours, the latter combined with scintigraphy, were performed according to the recommendations of IAEA (BELCHER et coll. 1964). Scanning was carried out with a conventional scanner equipped with a NaI(Tl)-scintillation detector (diameter 12.7 cm × 5.1 cm) and a 91 hole focussing collimator having a line-spread function with a resolution of approx. 9 mm for ^{131}I at the 9 cm focus. The counts were collected digitally using a cell size of 2 mm × 2 mm. Image-processing consisted of bounding and filtering with a Metz filter (11 × 11, FWHM = 9 mm, 6 iterations). The resulting image was plotted as an isocount map in full scale together with an isometric presentation (MÖLLER et coll. 1972). Since 1972 computer scintigraphy has been a routine investigation complementary to the conventional dot scintigraphy at this department. The examinations using $^{99}\text{Tc}^{\text{m}}$ were performed with a scintillation camera equipped with a pinhole collimator (diameter 4 mm). Data collection began 30 min after the intravenous administration of 70 MBq (approx. 2 mCi) $^{99}\text{Tc}^{\text{m}}$ pertechnetate.

A correlation between the routine dot scintigram and the same scintigram after computer-assisted image processing was performed in 45 patients.

The scintigrams were re-examined independently

by 2 of the authors without knowing the original report, and these results were then correlated to the macroscopic and microscopic findings. Almost complete agreement existed between the results of the original and revised examinations of the scintigrams.

In 73 patients fine needle aspiration biopsy was carried out preoperatively, guided by the findings at dot scintigraphy. The May-Grünwald-Giemsa staining method was used. All cytologic specimens have been re-examined. The reasons for obtaining a false negative finding were analysed further.

The patients were operated at the Department of Surgery or the Department of Otolaryngology. The size and localization of the tumour were estimated from the description during operation and measurements on the surgical specimen. In a few cases, mainly microscopic tumours, the size was estimated on the subsequent histopathologic examination. All microscopic slides have been re-examined by one investigator, and the tumours have been grouped according to the WHO classification (HEDINGER & SOBIN 1974).

Results

Scintigraphy—histopathology

The breakdown of the tumours into histologic subtypes in the 83 patients is presented in Table 1

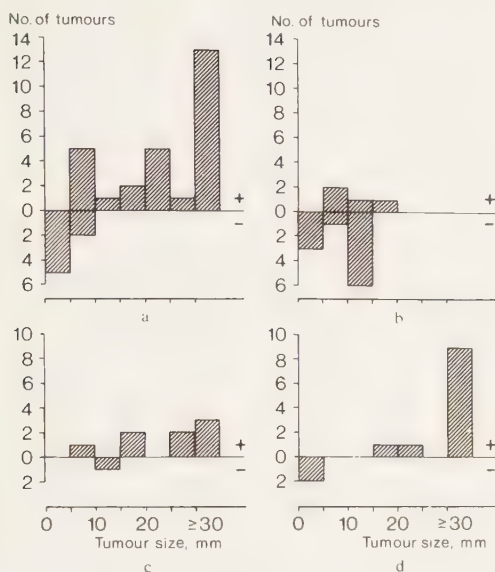


Fig. 1. Comparison between tumour size measured on the surgical specimen and the scintigraphically diagnosed (+) respectively missed (-) tumours. (Cases with irregular scintigraphic uptake or tumour of unspecified size or with uncertain location have been excluded.) a) Well differentiated carcinomas. b) Hereditary MCT without symptoms. c) Sporadic MCT and hereditary MCT with symptoms. d) Undifferentiated tumours.

together with the scintigraphic appearance. Of the 83 scintigrams, 50 showed a solitary area with absent or decreased uptake within one lobe, while similar changes were present in both lobes in 8 scintigrams. Eighteen scintigrams showed irregular uptake and 7 scintigrams were normal.

Well differentiated carcinoma. Well differentiated thyroid carcinomas were present in 54 of the 83 patients (65%). Histologically, 6 patients had a follicular carcinoma, 28 a papillary carcinoma and 20 a mixed type of carcinoma (papillary carcinoma with a follicular component). There were no significant differences in age distribution between these 3 groups.

The signs or symptoms which motivated the thyroid scanning were as follows: In 41 patients it was a thyroid nodule or a nodular goitre, in 11 patients metastases in the cervical nodes from a thyroid carcinoma, in one patient a vocal cord paralysis and in one patient a mediastinal mass detected at chest radiography.

Forty-five patients were examined with ^{131}I , 5

with $^{99}\text{Tc}^{\text{m}}$ pertechnetate and 4 with both radionuclides.

In 35 patients the thyroid scintigrams showed a solitary area in one or both lobes with reduced uptake. Fifteen patients had an irregular uptake, and 4 scans were normal. Of the 4 patients investigated both with ^{131}I and $^{99}\text{Tc}^{\text{m}}$ pertechnetate, the scintigrams did not differ in 3 cases while in the fourth a small papillary carcinoma which did not appear on the iodine scintigram could be identified as a small defect in the technetium scintigram.

Of the 30 patients who had a solitary reduced or absent uptake in one lobe, 25 patients were operated upon with total thyroidectomy and 5 with lobectomy. Histologically, a carcinoma was revealed in 29 of the 30 patients, corresponding to the area of reduced uptake in the scintigram. In the remaining patient the reduced uptake corresponded to a benign lesion while a carcinoma 5 mm in diameter was detected in the scintigraphically normal lobe.

In 5 patients a solitary reduced uptake was noticed in both lobes. Three of these had bilateral carcinomas corresponding to the scintigraphic findings. In the remaining 2 patients the carcinoma was confined to one lobe only and the reduced uptake in the other lobe corresponded to a nodular goitre.

In 7 patients with histologically confirmed bilateral carcinoma but with a solitary reduced uptake in one lobe only, the scintigraphically normal contralateral lobe revealed a tumour with a diameter of less than 5 mm in 5 patients and with a diameter between 5 and 10 mm in 2 patients.

In 15 patients the thyroid scintigram presented an irregular uptake. Out of these, 6 patients had bilateral carcinoma and 8 patients carcinoma confined to one lobe. In one patient only lobectomy was performed.

In 4 patients with normal scintigrams 2 had small carcinomas with a diameter of less than 10 mm, and the scintigraphy was performed due to cervical metastases. The other 2 patients had larger papillary carcinomas; one was 25 mm in diameter and located in the pyramidal lobe, and the other patient had a mediastinal mass detected at chest radiography.

The relation between tumour-size and scintigraphic detectability is shown in Fig. 1a. Twenty-seven out of the 34 differentiated tumours were detected by scintigraphy. The 7 tumours not seen in the thyroid image were all less than 10 mm. Tumours of unspecified size or with uncertain location

have been excluded in this analysis as well as scintigrams showing an irregular uptake. However, in some cases with irregular uptake at scintigraphy there was a distinct reduction in uptake corresponding to the tumour site.

Medullary carcinoma. Sixteen of the 83 patients (19%) had medullary carcinoma (MCT; Table 1). Nine of these patients were scanned due to local clinical disease. This group included patients with sporadic MCT ($n=5$), as well as hereditary MCT with symptoms ($n=4$). Seven patients without symptoms were investigated for hereditary MCT as a part of a screening procedure. The thyroid image in the group with manifest disease showed a 'cold' nodule in all but one patient. In the 'screening group' only 4 patients had abnormal scintigrams.

In sporadic MCT bilateral tumours were not revealed at histologic examination except in one patient who had a scintigraphic irregular uptake. In the 4 patients with hereditary MCT with symptoms histopathology revealed bilateral tumours in all cases. All of the screened patients with hereditary MCT had bilateral tumours.

The relation between tumour-size and detectability at scintigraphy is shown in Fig. 1b and c. Tumours of unspecified size or with uncertain localization as well as those associated with irregular uptake have been excluded. Only one tumour with an approximate diameter of 10 mm was not detected at scintigraphy in the group of sporadic and hereditary MCT with symptoms. In the 'screening group', however, most tumours were not diagnosed scintigraphically. In 6 cases of this group the undiagnosed tumours ranged in size between 10 and 15 mm.

Undifferentiated carcinoma. Undifferentiated thyroid carcinomas comprised 13 of the 83 patients (16%). The histologic subdivisions are presented in Table 1. The initial symptom in 12 of the patients was a growing thyroid gland and in one patient a vocal cord paralysis.

All these patients were examined with ^{131}I scintigraphy. In 11 patients a markedly reduced uptake corresponding to a palpable tumour was demonstrated. In 2 patients, one with a lymphoma and one with an unclassified anaplastic carcinoma, an irregular uptake was found. Only 5 patients were operated upon in the entire group. In the other 8 patients with larger tumours the diagnosis was established at open biopsy. The correlation between scintigraphic findings and the tumour-size is illustrated in Fig. 1d (scintigrams with irregular uptake

Table 2

Scintigraphic appearance and preoperative aspiration cytology in 73 patients

Cytology	Scintigraphic appearance			No.
	Solitary reduced uptake	Irregular uptake	Normal uptake	
Carcinoma	26	2	1	29
Possible carcinoma	12	6	1	19
Benign	14	6	2	22
Not evaluable	2	1	—	3
Total	54	15	4	73

Table 3

Result of re-evaluation of 22 patients with false negative preoperative aspiration cytology

The tumour was not needed	11
Predominantly cystic papillary carcinoma, no carcinoma cells in the aspirated fluid	3
Technically inferior aspirate with few cells and no malignant cells	3
Cytologic misinterpretation of papillary carcinoma	3
Cytologic misinterpretation of follicular carcinoma	2

Table 4

Comparison between dot scintigraphy and computer-assisted scintigraphy in 45 patients

Dot scintigraphy	Computer scintigraphy			No.
	Inferior	Equal	Superior	
Normal	—	6	—	6
Defect in one or both lobes	2	18	7	27
Irregular uptake	—	5	7	12
Total	2	29	14	45

are excluded). Only 2 microscopic carcinomas, observed in the contralateral lobe during histopathologic examination, were not diagnosed.

Scintigraphy—preoperative aspiration cytology

Preoperative aspiration cytology from the thyroid was performed in 73 patients (Table 2). In 48 patients (66%) the preoperative cytologic diagnosis was carcinoma or possible carcinoma.

The aspiration cytology was not evaluable in 3 cases because the smears contained only blood or too few epithelial cells for a diagnosis of malignancy. In 22 patients (30%) the preoperative cytology gave a false benign diagnosis. These specimens have been re-evaluated and the result is analysed in Table 3.

The most common cause of a false benign cytodiagnosis was that the tumour was not hit at needling. This occurred in 11 patients. These patients included 7 with occult (diameter <15 mm) papillary or mixed carcinomas, 3 with occult medullary carcinomas, investigated as a part of a screening for hereditary MCT, and one with undifferentiated tumour with a diameter of 20 mm. In 5 patients with not needled papillary carcinomas the preoperative scintigrams demonstrated an irregular uptake while in 2 patients with MCT the scintigrams were normal.

In 3 patients with false benign cytodiagnosis a cystic papillary carcinoma was present whereas the aspiration smear only contained cystic fluid without malignant cells.

A cytologic misinterpretation was made in 5 patients; 3 of these had a papillary carcinoma and 2 had follicular carcinoma.

Dot scintigraphy—computer scintigraphy

A comparison of the diagnostic information in the routine dot scintigraphy and the computer-processed scintigraphy was performed in 45 patients (Table 4).

The computer-processed images were superior to the dot scintigrams with respect to detection of solitary reduced uptake in 7 of 27 patients (Fig. 2) and inferior in only 2 of 27 patients. However, in no case the conclusions derived from the different image presentations were divergent. Multinodular lesions of the thyroid gland were apparently more distinct with the computer-assisted scintigraphy.

Discussion

The preoperative diagnosis of thyroid carcinoma has still considerable weak points. In typical cases the diagnosis is quite easy but there is no doubt that the early diagnosis may be extremely difficult. It is therefore absolutely necessary to consider all the clinical factors and fully exploit the available techniques to make the preoperative diagnosis as correct as possible to avoid needless operations.

As mentioned previously, the incidence of thyroid

carcinoma in solitary 'cold' nodules is relatively high, approximately 20 per cent (KENDALL & CONDON 1969). The risk seems to be even higher in the age group below 40 (BURROW *et coll.* 1978). However, other reports (KATZ & WARREN 1976) suggest that the risk increases with age. The frequency data are often based on small and selected materials and vary between 3 and 43 per cent (SHIMAOKA & SOKAL 1964, HOFFMAN *et coll.* 1972). On the other hand, there is little information on how often a carcinoma does present itself as a solitary cold defect, and if there are any specific differences in the scintigraphic appearance of the different histopathologic types.

In the present investigation the most common finding in the scintigrams of patients with subsequently confirmed carcinoma was a solitary area with absent or reduced uptake. This occurred in approximately 70 per cent of the scintigrams from the entire group of patients, and in 65 per cent of all scintigrams in patients with a well differentiated thyroid carcinoma. In the undifferentiated carcinomas practically all scintigrams revealed a markedly reduced uptake in the affected lobe, which in most of the cases was not even possible to delineate. In the small group of medullary carcinomas with manifest disease a solitary reduced uptake was the most common finding, whereas the scintigram was normal in several cases in the 'screening group'.

The size of the lesion is an important factor in preoperative estimation. Lesions smaller than 10 to 15 mm in diameter are usually not evident by palpation. WOOLNER *et coll.* (1961) arbitrarily defined a tumour of papillary type less than 15 mm in largest diameter as 'occult' carcinoma. The present investigation demonstrated that scintigraphy cannot resolve lesions smaller than approximately 5 mm, but no well differentiated carcinomas exceeding 10 mm were missed, apart from those located outside the thyroid lobes or associated with a scintigram with irregular patchy uptake.

Using $^{99}\text{Tc}^{\text{m}}$ pertechnetate and a gamma camera PINSKY & RYO (1977) showed that in no case lesions smaller than 4 mm could be detected on the scintigram. In the same series the largest malignant nodule missed by scintigraphy was a 15 mm papillary carcinoma located in the isthmus, whereas the largest unidentified malignancy located in the lobe was 12 mm in diameter.

In the present investigation, for patients belonging to the group of hereditary MCT without symp-

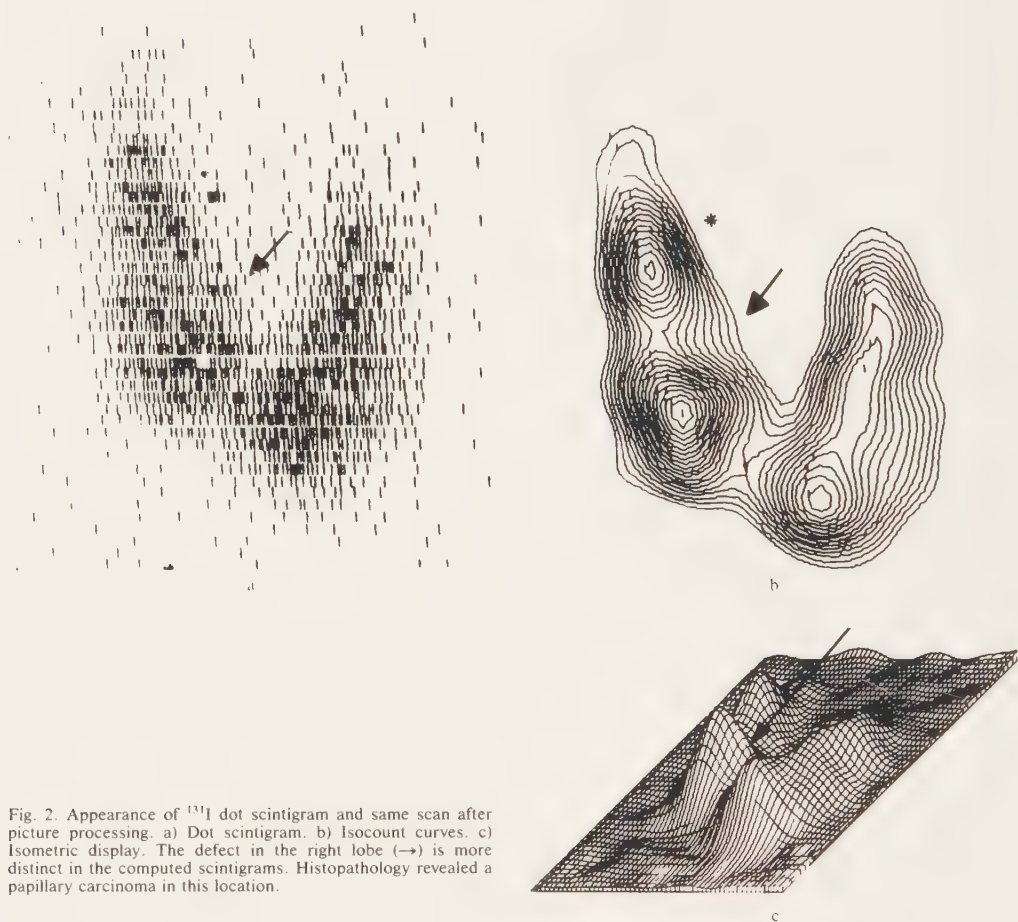


Fig. 2. Appearance of ^{131}I dot scintigram and same scan after picture processing. a) Dot scintigram. b) Isocount curves. c) Isometric display. The defect in the right lobe ($\rightarrow$) is more distinct in the computed scintigrams. Histopathology revealed a papillary carcinoma in this location.

toms, tumours could not usually be detected on thyroid scintigraphy, though in 6 cases the tumour size ranged between 10 and 15 mm. In a recent report of mainly non-familial MCT (RASMUSSEN 1982) 6 of 29 (21%) cases had a normal uptake of $^{99}\text{Tc}^{\text{m}}$ or ^{131}I though the diameter of the tumour exceeded 15 mm. It is an unexpected finding that the iodine scintigraphy is less sensitive in detecting MCT than other thyroid neoplasms, and is in contrast to the autoradiographic examinations by LJUNGBERG (1966), which could not demonstrate uptake of radioiodine neither in MCT tumour cells nor in the stromal amyloid produced by these. For diagnosing MCT biochemical tests are superior to

scintigraphy of the thyroid. Thus, TELENUS-BERG et coll. (1977) have reported that $\Delta\text{S-calcitonin}$ (the increase in the serum level of calcitonin (the increase in the serum level of calcitonin after administration of pentagastrin) will confirm the presence of even very small occult tumours or metastases. As a screening procedure for MCT this method should be preferred principally. The problem is, however, to localize biochemically detected occult MCT. At present there seems to be no reliable non-invasive method available.

In the group of undifferentiated carcinomas there were no problems in making a correct assumption from the scintigram, which often showed a nearly

total disappearance of isotope uptake in the affected lobe (TENNVALL *et coll.* 1979).

The isocount and isometric presentations of the thyroid scan after computer-assisted picture processing were superior to the dot scintigram with respect to detection of localized areas with reduced uptake in 7 of 27 (26%) cases. It was inferior in only 2 patients. In a previous report the computer scintigram was found to be superior in 27 of 44 (61%) cases with respect to detection of solitary areas with reduced uptake (MÖLLER *et coll.* 1973). Irregular uptake is also more clearly identifiable on computer scintigrams. These 2 investigations thus indicate that computer-processing of scintigraphic images gives additional valuable information in the diagnosis of thyroid carcinomas. Furthermore the administered activity could often be reduced to approximately 0.37 MBq (10 μ Ci) ^{131}I without deterioration in image quality and with a significant reduction of absorbed dose to the thyroid as a result. These advantages could be substantiated further by using $^{99}\text{Tc}^{\text{m}}$ pertechnetate and a gamma camera. However, this radiopharmaceutical, which is trapped by the thyroid but is not involved in the hormone synthesis, has several disadvantages. For example, the uptake in the salivary glands is relatively high and the contaminated saliva that is swallowed can give rise to artifacts. In addition, there is sometimes a relatively high background in the blood pool of the neck, which can impair the image quality. For diagnosing thyroid carcinoma the main disadvantage of $^{99}\text{Tc}^{\text{m}}$ is possibly the inconstantly increased uptake in some tumours, especially follicular carcinomas (ERJAVEC *et coll.* 1977). The enhanced uptake thus simulates toxic nodules, which can mislead the interpreter, since as a practical clinical rule a true toxic nodule does not harbour a carcinoma. In the present investigation no neoplasms were proven to be hyperfunctioning nodules.

From the point of view of iodine metabolism and the possible improvements of the spatial resolution of the imaging system the most ideal radionuclide for investigation of the thyroid is ^{123}I (ATKINS *et coll.* 1973, CEDERQUIST *et coll.* 1975). At present it is, however, rather expensive for routine use at most centres. $^{99}\text{Tc}^{\text{m}}$ has the advantage of giving a low radiation dose to the thyroid and the possibility of imaging a short time after administration. By using a gamma camera and oblique views it is possible to increase the accuracy of detection and localization of cold nodules.

In attempts to find an agent capable of differentiating malignant nodules from benign ones in the thyroid, several radionuclides and radiopharmaceuticals have been used with varying degree of success, e.g. ^{131}Cs (MURRAY *et coll.* 1970) and ^{75}Se -methionine (WEINSTEIN *et coll.* 1971). It is reported that ^{67}Ga -citrate shows affinity for anaplastic carcinoma and lymphoma of the thyroid (HIGASHI *et coll.* 1981, SENGU *et coll.* 1982). ^{201}Tl -chloride has currently been reported to be an excellent agent for detecting well differentiated thyroid carcinoma (SALVATORE *et coll.* 1976), but several investigators have reported increased uptake in tumour as well as in other thyroid lesions (PALERMO *et coll.* 1979, HARADA *et coll.* 1980). However, also by taking the disappearance rate into account it will give an increased specificity for tumour detection (TENNVALL *et coll.* 1981).

Despite the fact that scintigraphy is a rather unspecific method, MAISEY (1981) estimated that approximately half of the patients with thyroid nodules can be spared unnecessary operations by undergoing a simple sequence of non-invasive investigations. However, he is not emphasising that thyroid scintigraphy is a clinical method and, if also such factors as age and sex are taken into account, the probability of making a correct diagnosis is further increased. In addition the usefulness of thyroid scintigraphy will be even more justified in combination with aspiration cytology.

Aspiration cytology is a more specific method, but it too has several limitations. The preoperative cytodiagnosis gave a false benign diagnosis in 22 of 73 patients (30%) in the present series. This is a large number in comparison with other reports (LÖWHAGEN *et coll.* 1981). Half the number of these cases consisted of 'missed' tumours not hit at the needling. However, the size of these was generally rather small (diameter <15 mm). In addition, in 7 of these patients, the scintigram showed either an irregular uptake or a normal image, and therefore the dot scintigram was not a helpful guide for the cytologist. The computer-processed scintigrams were usually not available at the needling.

The cystic tumours are always a problem as the cystic fluid often contains macrophages and inflammatory cells. Routinely the cyst was drained and afterwards any palpable nodule was needled. Even with this procedure it might be very difficult to diagnose a carcinoma. The cytologic distinction between follicular adenoma and follicular carcinoma is

very difficult (LÖWHAGEN & SPRENGER 1974). In general the cytologic difference between benign and malignant follicular tumours is often so subtle that the policy has been to state the cytologic diagnosis as 'follicular neoplasm' without specifying its benign or malignant character, with the understanding that surgery should be performed for histopathologic diagnosis.

SUMMARY

At preoperative scintigraphy of 83 consecutive histopathologically confirmed thyroid carcinomas a solitary reduced uptake was observed in 70 per cent. The minimum detectable size was 10 mm for differentiated carcinomas showing this image, but in the 'screening group' of hereditary medullary carcinoma several scintigrams were considered normal despite a tumour size of 10 to 15 mm. In the imaging of the undifferentiated carcinoma a solitary reduced uptake with disappearance of the entire affected lobe was often demonstrated. Multifocal areas in the dot scintigram representing tumours were often missed at fine needle aspiration biopsy. Computer-processed scintigrams were superior in showing multifocal lesions.

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SENSITIVITY AND SPECIFICITY
OF FINE-NEEDLE ASPIRATION CYTOLOGY
IN THE DIAGNOSIS
OF TUMOURS OF THE THYROID GLAND

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ABSTRACT

In a large study of consecutive patients with either malignant (n=203) or benign tumours (n=217), fine-needle aspiration cytology (AC), which was used as a routine method for evaluating thyroid tumours, was found to have a sensitivity of 0.57 and a specificity of 0.98.

The sensitivity of AC in the diagnosis of medullary and undifferentiated carcinomas was found to be 0.82 and 0.84 respectively. None of these tumours was microscopically misdiagnosed.

In contrast, the sensitivity for papillary carcinomas was only 0.58 (occult carcinoma excluded) and for follicular carcinoma 0.42. Four reasons for these low sensitivity values were identified: the tumour was missed at aspiration, microscopic misinterpretation, the diagnosis of cellular atypia, and indeterminate cytodiagnosis.

The re-evaluation of false diagnoses once more proved the diagnostic problem to distinguish follicular adenomas from follicular carcinomas. Microscopic misses in papillary carcinomas were due to either misinterpretations of characteristic cytomorphologic features or the smears were judged as atypical when papillary formations were missing and only one or two of the other cellular criteria appeared.

The specificity was found to be high enough to permit surgical intervention after a cytodiagnosis of malignancy.

INTRODUCTION

In the diagnosis of primary tumours of the thyroid gland patient and family history, physical examination, thyroid function tests, thyroid scintigraphy and ultrasonography have been employed for many years (Maisey, 1981; Aschcraft & v.Herle, 1981). Since the introduction of fine-needle aspiration cytology (AC) there has been increasing interest in including this method as a routine preoperative diagnostic tool for these tumours (Söderström, 1952; Einhorn and Franzén, 1962; Löwhagen et al., 1979, 1981; Block et al., 1980; Norton et al., 1982; Brauer et al., 1984). However, most reports include only a limited number of patients with primary malignant or benign tumours of the thyroid gland, and therefore evaluation of the sensitivity and specificity of the method has been difficult (Aspegren et al., 1976; Hamaker et al., 1983; Hamberger et al., 1982; Kini et al., 1980; Miller et al., 1981; Suen & Ouenville, 1983).

The sensitivity $[(\text{true positive})/(\text{true positive} + \text{false negative})]$ gives the probability for the method to detect a thyroid malignancy while the specificity $[(\text{true negative})/(\text{true negative} + \text{false positive})]$ gives the probability for the method to confirm a malignant thyroid mass. The percentage of correct positive diagnosis is expressed as a positive predictive value $[(\text{true positive})/(\text{true positive} + \text{false positive})]$.

In the present study a large number of consecutive patients with either primary malignant or benign tumours of the thyroid gland was examined by preoperative AC and the cytodiagnoses were correlated to the histologic diagnoses from the surgical specimens.

The aim of the study was to evaluate the sensitivity and specificity of preoperative AC in the diagnosis of tumours of the thyroid gland.

MATERIALS AND METHODS

Patient material

During the period from 1968-1981, 203 consecutive patients with a histopathologic diagnosis of a primary malignant thyroid tumour underwent a preoperative AC and the smears were analyzed at the University Hospital of Lund. Patients in whom the initial diagnosis was established by AC from regional or distant metastases were not included in the material. Patients with medullary thyroid carcinoma, but without thyroid enlargement, verified by biochemical tests, were also excluded. Of the patients in this study 148 were females and 55 males ($\%:\sigma = 2.7:1$) with a median age of 54 years (age range, 14-88).

In order to compare the data from this group of patients with malignant tumours to preoperative aspiration in patients with benign thyroid tumour (follicular adenoma, nodular goitre or chronic thyroiditis) with approximately the same number of patients with a histopathologic benign thyroid tumour during the period from 1980-1981 were analyzed. Since 1980 all histopathologic and cytologic diagnoses have been coded according to the SNOMED (Systematized Nomenclature of Medicine) nomenclature and computer registered. Thus the benign thyroid tumour data were obtained by searching the computer file. This search located a group of 276 consecutive patients who had a histopathologic diagnosis of benign thyroid tumours and of these, 217 patients were found to have had a preoperative AC. The proportion of females to males was 3.7:1, with a median age of 46 years (age range, 14-80).

Pretreatment examination

All patients were evaluated with history, physical examination and thyroid function tests. In 152 patients in the malignant series preoperative scintigraphy was performed with iodine-131 or technetium-99m. In the period from 1968-1975, 68 of 96 patients were studied with thyroid scintigraphy, and during the period from 1976-1981 scintigraphy was carried out in 84 out of 107 patients. Scintigrams with solitary "cold" areas usually served as a guide at needling. Since 1977 selected patients with a scintigraphically solitary "cold" nodule were also investigated preoperatively with thallium-201 scintigrams often extended with dynamic studies. The results of conventional as well as of thallium scintigraphy studies have been reported separately (Tennvall et al., 1981, 1983, in press).

Fine-needle aspiration cytology procedure and staining methods
AC was introduced as a routine test in 1963 at the Department of Cyodiagnosics, University Hospital of Lund. During the study period from 1968-1981, 18 different cytopathologists performed the aspirations and/or evaluation of the smears for this study. The degree of experience in cytopathology varied between cytopathologists ranging from a few months to several years. One of the cytopathologist (MÅ) had diagnosed 88 of the present malignant tumours in contrast to others, who only diagnosed a few. However, all cytopathologists had at least 2 years training in clinical pathology before starting with cytology.

In 168 patients the needlings were carried out by the cytopathologists who afterwards analyzed the aspirate, and 35 patients were aspirated by clinicians. The needlings were performed with a 22 gauge needle (outer diameter 0.6 mm) without local anaesthetics.

During the first years of the study the aspirates were fixed in alcohol and stained with haematoxylin-eosin (HE), but from 1973-1974 one or several air-dried smears were added for May-Grünwald-Giemsa (MGG) staining. During the last years of the study MGG was used almost exclusively. The Papanicolaou staining method was not used. In re-evaluation of the present material the aspiration was considered as an "aspiration miss" if the tumour was not hit at needling. At microscopy the tumour cells could have either been overlooked or misinterpreted. Both these causes were defined as a "microscopic miss".

The cytodiagnoses were classified as malignant tumour, suspected for malignant tumour, cellular atypia, indeterminate, benign aspirate and not evaluable. The first two categories were always considered positive for a malignant diagnosis and led always to surgery. All other cytologic findings were classified in the present report as negative for malignancy. Indeterminate diagnosis equals the diagnosis of follicular neoplasm. Since 1974-75 the cytopathologists in the laboratory increasingly used this diagnosis for cellular aspirates with follicle-like structures made up of cells with more or less pronounced anisocytosis and anisokaryosis, different degrees of hyperchromasia and occasional prominent nucleoli. This diagnostic term came into use when Löwhagen and Sprenger (1974) published their detailed paper on the cytodiagnosis of follicular adenoma versus follicular carcinoma. The cytodiagnosis was considered not evaluable when the aspiration did not yield a sufficient number of cells for analysis.

Surgical resection

After the preoperative examination procedures mentioned above, surgery was performed. The size of the tumours was estimated from the surgeon's operative-records, the histopathologic forms or from the slides. In the latter case the tumours were considered to have shrunk by approximately 25%. Thus a size correction was made. Tumours 10 mm or less in their greatest diameter were considered to be occult (UICC, 1978).

Histopathology

The histologic slides were routinely stained with HE. The malignant tumours were classified according to the criteria of the WHO International Histological Classification for Thyroid Tumours (Hedinger and Sobin, 1974).

RESULTS

The primary cytodiagnoses in the material taken from malignant tumours are presented in Table I. From figures based on these findings, the sensitivity was calculated for all the tumour material and for the individual histologic groups (Table II).

Table I: Primary cytodiagnosis in 203 histologically verified primary malignant tumours of the thyroid gland, treated 1968-1981

CYTODIAGNOSIS	HISTOLOGICAL DIAGNOSIS				
	Papillary carcinoma	Follicular carcinoma	Medullary carcinoma	Undiff. Carcinoma	Malignant lymphoma
Malignant tumour (85)	42	5	12	19	7
Suspected for malignant tumour (30)	18	5	2	2	3
Cellular atypia (13)	9	4	-	-	-
Indeterminate (11)	9	2	-	-	-
Benign tumour (56)	43	6	4	1	2
Not evaluable (8)	2	2	1	3	-
Total (203)	123	24	19	25	12
	60.6 %	11.8 %	9.4 %	12.3 %	5.9 %

Table II: Sensitivity of aspiration cytology correlated to histopathology, in 203 patients.

Papillary carcinoma	0.49
Ditto, occult ca excluded	0.58
Follicular carcinoma	0.42
Medullary carcinoma	0.74
Ditto, occult ca excluded	0.82
Undifferentiated carcinoma	0.84
Malignant lymphoma	0.83
Total	0.57

Table III: Cytodiagnosis, classified as benign tumour in 56 patients, related to histologic diagnosis.

	No.	Papillary carcinoma	Follicular carcinoma	Medullary carcinoma	Undiff. carcinoma	Malignant lymphoma
Aspiration miss, tumour $\phi > 10$ mm	15	11	-	2	1	1
Aspiration miss, tumour $\phi \leq 10$ mm	21	19	-	2	-	-
Cystic tumour	4	4	-	-	-	-
Microscopic miss	16	9	6	-	-	1
Total	56	43	6	4	1	2

The study period was also divided into two time periods (1968-1975 and 1976-1981) with approximately the same number of patients as well as same proportions of histologic groups in each period in order to evaluate any fluctuations in sensitivity during the study period. However, the sensitivity showed insignificant variations between the two periods for all histologic groups.

The causes of the cytologic false benign diagnoses in relation to histologic diagnosis were re-evaluated (Table III).

In 24 patients with papillary (n=18) and follicular (n=6) thyroid carcinomas the preoperative cytodiagnosis was cellular atypia or indeterminate. When these diagnoses were reconsidered three of the 18 papillary carcinomas were found to be occult. In these three patients the aspiration was directed against a follicular adenoma. Six of the tumours with a cytodiagnosis of cellular atypia or indeterminate were found to be follicular carcinomas.

In the material from histologically confirmed benign thyroid tumours during the period 1980-1981 the final histologic diagnosis proved to be nodular goitres (n=116), follicular adenomas (n=79), a combination of these (n=15) and chronic thyroiditis (n=7). Only 1.8 per cent had a false positive cytology (Table IV). Thus the specificity for AC to confirm a malignant tumour was very high (0.98).

Table IV: Primary cytodiagnosis in 217 patients with histologically verified benign thyroid tumours.

Cytodiagnosis	No. of patients	
Malignant tumour	1	0.46 %
Suspected for malignant tumour	3	1.38 %
Cellular atypia	6	2.76 %
Indeterminate	20	9.21 %
Benign tumour	183	84.33 %
Not evaluable	4	1.84 %

The cytodiagnosis of the false malignant tumour was a papillary carcinoma. The histologic diagnosis was a cystic nodular goitre with pseudopapillary formations. The three smears suspected of malignancy were considered to be follicular carcinomas. The histologic diagnoses of these tumours were follicular adenomas.

At histologic examination of the six cases with cellular atypia the lesions were in three cases considered to be follicular adenomas and, in three cases, nodular goitre.

In the 20 patients with indeterminate diagnosis histopathology of the surgical specimens demonstrated follicular adenomas in 15 patients and nodular goitres in five patients.

During the period from 1980-1981 it was possible to match the two materials. Thus for this period it was also possible to calculate the positive predictive value, which showed to be 0.83 (19/23).

DISCUSSION

The definitive value of AC of thyroid tumours lies in selecting patients for operation (Block et al., 1980; Suen et al., 1983; Brauer et al., 1984). If AC reveals a carcinoma, surgery must be performed unless important medical contraindications are present, since a false positive AC is rare according to the present results and to results of other studies (Einhorn and Franzen, 1962; Löwhagen et al., 1979; Brauer et al., 1984).

A high reported incidence of malignancy among surgically treated patients reflects preoperative efforts in patient selection (Block et al., 1980; Suen et al., 1983). However, in these reports the number of false negative results has been very low because most of the cytologically benign cases were not operated on, which also meant that the reported sensitivity of AC was improved (Block et al., 1980; Norton et al., 1982). In the present study the surgical indications were based not only on cytodiagnosis but also on clinical judgement and, in most patients, on scintigraphy. Since the cold areas on preoperative scintigrams were in many patients a guide at needling, this procedure probably resulted in a decreased number of "aspiration-missed tumours" and thereby the sensitivity of AC was improved.

It is important when reporting results of AC to describe the proportion of occult carcinomas included in results, since these tumours (i.e. occult papillary carcinomas) often are found incidentally in or adjacent to a benign lesion and to a great extent are not hit at needling (Table II).

Block et al. (1983) stressed the importance of clarifying in what way cellular atypia and indeterminate cytodiagnosis were included in the results of AC, since in his material these cytodiagnoses were not infrequent (14%).

To provide an example if the classifications of cellular atypia and indeterminate were included in the malignant group, the sensitivity would increase to 0.68 but the specificity would at the same time decrease to 0.86.

It should be noted that this material from 420 patients with thyroid tumours is routine material, which means that all cytopathologists working in the laboratory participated in the needling of the patients as well as in the cytodiagnoses.

The sensitivity of AC in diagnosing medullary carcinomas (occult carcinoma excluded) as well as undifferentiated carcinomas was found to be high, 0.82 and 0.84, respective-

ly (Table II). In no case in these histologic groups was the tumour microscopically misdiagnosed (Table III). The cytologic features of these tumours are rather easy to discern, as discussed by Söderström et al. (1975) and Tennvall et al. (1979).

The present study demonstrated that the problem of AC lies in diagnosing papillary and follicular carcinoma (Tables I-III).

The most common cause of a false negative cytodiagnosis of papillary carcinoma was an aspiration miss. Most of the tumours not hit at needling were occult (Table III). Even if these tumours were excluded from the study material the sensitivity remained low (Table II) compared to other materials. In some patients the papillary carcinoma exceeded 10 mm in diameter but the tumour was nevertheless missed at aspiration.

Table III demonstrates that the problem of the cystic tumour existed only in papillary carcinomas. In these patients the aspirates consisted of fluid with scattered inflammatory cells and macrophages but without epithelial cells, and thus ought to be included in the not evaluable category. The diagnostic problem with cystic tumours is a generally accepted difficulty in aspiration cytology and, as a rule, repeated needling is performed in order to evaluate all fluid and, finally, aspiration against palpable remnants, if any, ought to be performed. When the false benign diagnoses were re-evaluated (Table III) most of the characteristic features of papillary carcinomas (Kini et al., 1980) were found (papillary tissue fragments, monolayered sheets, tissue fragments with or without follicular pattern, psammoma bodies and large multinucleated foreign-body-type giant cells). These features had originally obviously been overlooked or misinterpreted by the cytopathologist. Re-evaluation of some of these misdiagnosed papillary carcinomas early in the study period revealed pseudonucleoli (viz. cytoplasmatic inclusions in the nucleus), but before the report of Söderström and Biörklund (1973) this diagnostic phenomenon was not observed in our laboratory.

In most of the patients with papillary carcinomas and with a cytodiagnosis of atypia, however, the smears were judged as cellular atypia if only one or two of the important cytologic features were present. Thus only a few or a single monolayered sheet of tumour cells were present. Unequivocal papillary fragments were not found and pseudonucleoli were not noted or appeared only in scattered cells. Nine patients had an indeterminate diagnosis. In five the aspiration was not performed against the carcinoma, (three of them being occult), but against palpable tumours, which proved to be follicular adenomas. The other four carcinomas were misdiagnosed, and two of these had a predominantly follicular component.

It is of interest, and contrary to many other reports, that the sensitivity for papillary carcinomas was only 0.58 (occult carcinoma excluded). Four reasons are evident: aspiration miss, microscopic miss, indeterminate cytodiagnosis and the diagnosis of cellular atypia. Early in the study period, missed diagnoses were probably the result of lack of experience. In addition, papillary carcinomas with predominantly

follicular areas might be as difficult to diagnose as the follicular carcinomas (vide infra).

From Table III it is evident that false benign cytodiagnosis of all the follicular carcinomas was due to microscopic misses. In addition follicular carcinomas were cytologically misdiagnosed as cellular atypia and as indeterminate. The cytodiagnosis of cellular atypia implied for these lesions features such as anisocytosis, anisokaryosis, irregular chromatin pattern, hyperchromasia and prominent nucleoli.

In the series diagnosed of benign tumours (Table IV), some follicular adenomas were diagnosed as suspicion of follicular carcinomas, cellular atypia and as indeterminate. This finding confirms the diagnostic problem of distinguishing a follicular carcinoma from a follicular adenoma (Löwhagen and Sprenger, 1974).

Thus there is a need for supplementary investigations in order to avoid unnecessary diagnostic operations in patients with the cytodiagnosis of cellular atypia or indeterminate. Scintigraphic imaging, however, of a thyroid nodule with iodine-131 or technetium-99m may make a diagnosis of carcinoma highly improbable if the scintigram shows an accumulation of the radionuclide or autonomously functioning nodule. Technetium-99m may, however, in rare cases fail to show a cold area that would have been detected in iodine-131 (Alderson et al., 1976). Computerized morphometric measurements of aspirates from follicular neoplasms (Boon et al., 1982) or dynamic studies with thallium-201 (Tennvall et al., 1981, in press) may enhance the preoperative diagnosis.

Conclusion

- Fine-needle aspiration used as a routine preoperative method in the evaluation of thyroid tumours had a sensitivity of 0.57 and a specificity of 0.98.
- The differential diagnostic problem of follicular adenoma versus follicular carcinoma was once more proved.
- The papillary carcinomas (sensitivity of 0.58) were not as easy to diagnose as described in earlier reports.
- False diagnoses depending upon different factors are unavoidable when AC of thyroid tumours is used as a routine method and cytopathologists with varying degrees of training perform the needleings and cytodiagnosis, but in spite of that the specificity is high enough for an unequivocal diagnosis of malignancy to be sufficient for surgical intervention.

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Scintigraphic Evaluation and Dynamic Studies with Thallium-201 in Thyroid Lesions with Suspected Cancer

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Abstract. Scintigraphic studies of the thyroid with thallium-201 chloride were performed in 46 patients in whom the final diagnosis was established by histology. In dynamic studies of 36 patients, sequential imaging was performed the first 40 min after injection. A single exponential, $C_{exp}(-\lambda t)$, was fitted to each of the curves generated from apparently pathological and from normal regions in each patient, as determined by earlier conventional scintigrams. To minimize the effects of normal individual variations, the relation between pathological (p) and normal (n) regions in the same patient was emphasized and quantified by two parameters, namely the extrapolated zero-time intercept (C_p/C_n) and the time development ($\lambda_p - \lambda_n$) of the ratio of counting rates/unit area in the two regions. The turnover appears to be somewhat slower for pathological tissue than for normal tissue. Although this difference was significant on the 5% level for both cancer and adenoma as a group, only the relative disappearance rate ($\lambda_p - \lambda_n$) resolved cancer from adenoma and from goiter on the same level. All but one of the differentiated cancers had an increased uptake.

201 chloride for differentiated cancer (Salvatore et al. 1976; Palermo et al. 1979; Kyoichi et al. 1978). In this study, we have investigated the potential of thallium-201 in increasing the specificity of tumour detection by analyzing the images as well as the dynamic parameters.

Material and Methods

Patients. During the period from April, 1977, to September, 1979, 46 patients in whom the iodine or technetium scintigrams showed a solitary area with reduced uptake or no uptake at all were investigated with thallium-201. The diagnosis was established in all patients by histology (Table 1). The dynamic study comprised 41 patients; 5 of these were excluded in the study: one with a cystic lesion, two with medullary cancer, and two with benign lesions, where a satisfactory choice of the region of interest could not be made.

Imaging Procedure and Dynamic Studies. Scintigraphy was performed on a Pho/Gamma III HP scintillation camera with a 60° pin-hole collimator of aperture 4.7 mm. Window setting was 35% at 75 KeV. Patients were given 1 mCi (37-74 MBq) thallium-201 chloride intravenously. Sequential imaging with 2 min intervals and digital storage (64 × 64) was performed the first 40 min after injection.

Regions of interest were selected on the basis of defects in earlier iodine-131 or technetium-99m images. A corresponding region could usually be identified in the sum of the thallium images. One apparently normal region in the thyroid was also chosen in each patient (Fig. 1). All patients were subsequently operated on

Introduction

In attempts to find an agent for differentiating malignant nodules from benign ones in the thyroid, several radionuclides and radiopharmaceuticals have been used with a greater or lesser degree of success (Murray et al. 1970; Weinstein et al. 1971). All of them have shown an accumulation even in benign lesions. Some of them, however, showed more specificity for certain types of cancer: for example, gallium-67 citrate for anaplastic cancer (Kaplan et al. 1974) and thallium-

Table 1. Histological diagnosis of solitary cold nodules

Histological diagnosis	No. of patients
Papillary carcinoma	7
Follicular carcinoma	2
Medullary carcinoma	2
Follicular adenoma	22
Nodular goiter	8
Cysts or hematoma	5
Total	46

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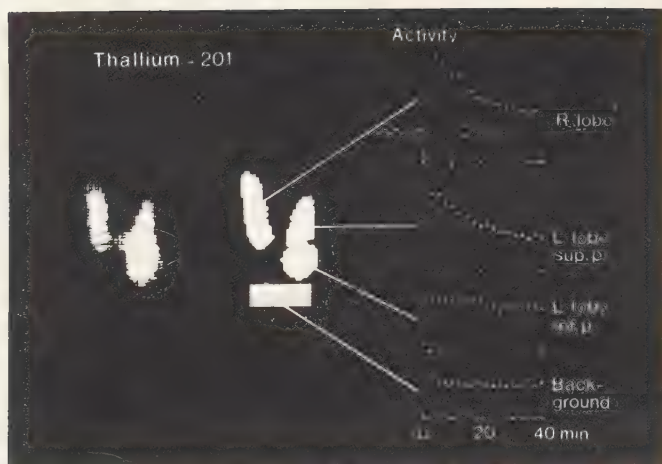


Fig. 1. Images of the thyroid with thallium-201 and counting rate curves for selected regions of interest. Dynamic parameters were calculated by taking the quotient of single exponentials fitted to background-subtracted and area-normalized data from pathological and normal regions

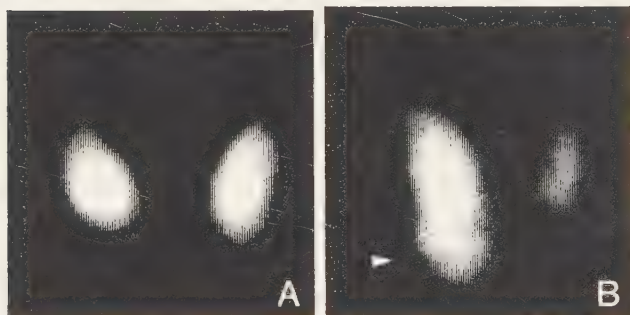


Fig. 2A, B. Apparently normal technetium-99m scintigram (A). Thallium-201 uptake extends outside the technetium image of the right lobe (arrow) (B)

and in no case did the histopathology invalidate the choice of regions. In some cases the thallium uptake in the suspected region was extended to a part of the affected lobe, which was not visible on the conventional scintigrams (Fig. 2).

A single exponential, $C \exp(-\lambda t)$, was fitted to each of the area-normalized and background-subtracted counting rate curves generated from the pathological and normal regions. The counting rate was approximately 5 counts/picture element/min in the selected part of the thyroid image, giving an uncertainty of about $\pm 5\%$ in the parameters C and λ . The initial rapid phase was avoided in the fits by using only data from 8 min after injection. To minimize the effects of the normal individual variations, the relation between pathological (p) and normal (n) regions in the same patient was emphasized. This was quantified by taking the ratio of the two exponentials describing the counting rate/unit area in the two regions, and expressed by (C_p/C_n) , representing the zero-time intercept ratio, and by (λ_p/λ_n) , representing the time development of the ratio. A negative value of (λ_p/λ_n) implies an extended effective half-life in the pathological region. The application of the ratio (C_p/C_n) minimizes errors due to the distance dependence of the collimator efficiency and due to attenuation, which might otherwise each be of the order of $\pm 10\%$. It also generally reduces the corrections necessitated by the radial depen-

dence of the collimator efficiency, which were typically less than 10%.

Results

Image Interpretation

Malignant Lesions. The papillary and follicular carcinomas showed an increased uptake of thallium-201 in five patients. In three patients, the uptake was equal to that in the normal thyroid regions. Only one case with differentiated carcinoma showed a decreased uptake of thallium. The two patients with medullary carcinomas had an accumulation of thallium-201 corresponding to that of normal thyroid tissue. Most of the carcinomas yielded images similar to that from a young man with papillary carcinoma (Fig. 3).

Cervical lymph node metastases were present in five patients with papillary carcinoma. In three there

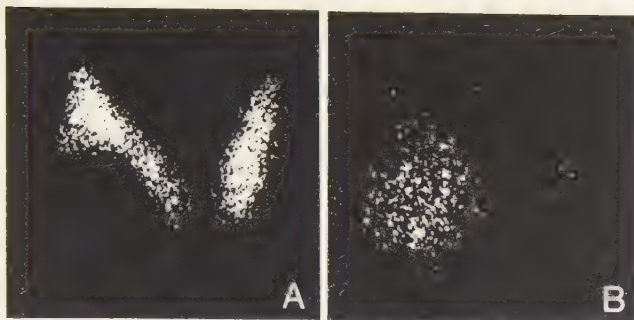


Fig. 3A, B. Defect in the right lobe on the technetium-99m image (A), but increased uptake of thallium-201 (B). Papillary carcinoma



Fig. 4. Thallium-201 image with marked uptake below the left thyroid lobe corresponding to histologically confirmed lymph-node metastasis from a papillary carcinoma less than 1 cm in diameter in the upper part of the left lobe

was an uptake of thallium-201 in the metastatic nodes (Fig. 4). The localizations were confirmed at operation, and the diagnosis was proven by histology. The two other cases with no uptake of thallium-201 were cystic metastases. None of the metastatic nodes showed any uptake of either iodine-131 or of technetium-99m. In the patients with follicular and medullary carcinomas, no accumulation of thallium-201 was seen in the neck outside the thyroid, and the operation revealed no cervical metastases.

A bone metastasis was seen in one patient with follicular carcinoma. The routine examination with iodine-131 showed uptake above the left knee, and cytology revealed small follicle cells. The primary tumor as well as the bone metastasis showed a high uptake of thallium-201. A bone-scintigram with EHDP showed an increased uptake in the bone lesion, but with a different distribution than with thallium (Fig. 5).

Benign Lesions. Most adenomas ($n=22$) showed a high uptake and belonged, with two exceptions, to the microfollicular or the Askenazy cell group. Five follicular adenomas with low uptake were either cystic, saturated with colloid, or showed signs of bleeding. In seven patients the histopathology revealed multinodular goiter, but both the thallium and the technetium scintigram showed a solitary area with reduced uptake corresponding to a nodule. One patient, earlier operated on with left lobectomy, had noticed a nodule in the midline of the neck that had enlarged over a period of time. The technetium scintigram showed an autonomous adenoma in the isthmus region and a totally suppressed right lobe. The thallium uptake was nearly equal in the isthmus adenoma and in the right lobe. One patient with nodular goiter was examined with thallium-201 during thyroxine treatment. The image of the thyroid was similar to that obtained with technetium-99m before the thyroxine treatment.

Dynamic Studies. The dynamic parameters for the 36 patients with histologically determined lesions shown as solitary reduced uptake on a conventional scintigram, are given in Table 2. In this representation (rate constant and logarithm of uptake ratio) individual values are more nearly normally distributed than the half-life and uptake ratio itself. The apparently normal thyroid tissues in these patients have a rate constant $\lambda_p = 0.028 \pm 0.009 \text{ min}^{-1}$, irrespective of the type of lesion in the affected lobe (there is no statistical difference on the 20% level). This value corresponds to a half-life of $25 \pm 8 \text{ min}$. The values for cancers, adenomas, and nodular goiter correspond to half-lives of 46 ± 22 , 30 ± 13 , and $28 \pm 9 \text{ min}$, respectively. The turnover thus appears to be somewhat slower for pathological tissues than for normal tissues (Fig. 6). This difference is significant on the 5% level for both cancer and adenoma. Only the relative disap-



Fig. 5A, B. Increased uptake of thallium-201 above the left knee on the postoperative whole-body scintigram (A). Increased uptake of technetium-99m-EHDP in the same region, but with a different distribution (B). Bone metastasis from follicular carcinoma

Table 2. Dynamic parameters. Mean $\pm$ SD

Histological diagnosis	No. of patients	Rate constant λ_p (min^{-1})	Relative disappearance rate $\lambda_p - \lambda_n$ (min^{-1})	Log uptake ratio $\ln(C_p/C_n)$
Carcinoma	7	0.015 ± 0.007	-0.017 ± 0.015	0.13 ± 0.40
Follicular adenoma	22	0.023 ± 0.010	-0.005 ± 0.011	0.26 ± 0.54
Nodular goiter	7	0.025 ± 0.008	0.00 ± 0.005	0.31 ± 0.61

Normal rate constant (36 patients) $\lambda_n = 0.028 \pm 0.009 \text{ min}^{-1}$

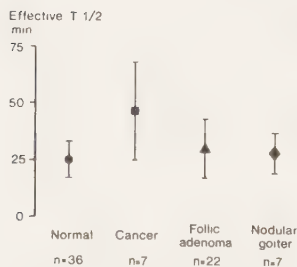


Fig. 6. Effective half-lives of thallium-201 in normal thyroid tissue and different thyroid lesions

pearance rate ($\lambda_p - \lambda_n$), however, distinguishes cancer as a group from adenoma and from nodular goiter on the same level. The differences shown for the uptake levels, $\ln(C_p/C_n)$, are not significant.

If the affected lobe was considerably enlarged, which occurred mostly in patients with follicular adenoma and nodular goiter, the uptake ratio was usually increased. When patients in whom the ratio between the areas of the abnormal and the normal lobes exceeded 2:1 were excluded, there was a tendency to higher relative uptake in the cancer group. The resulting changes in average uptake ratios are shown in Table 3. The values in this table correspond

Table 3. Uptake ratios^a

Histological diagnosis	No. of patients	Log uptake ratio $\ln (C_p/C_n)$
Carcinoma	5	0.240 ± 0.43
Follicular adenoma	16	0.032 ± 0.45
Nodular goiter	4	-0.061 ± 0.44

^a Grossly asymmetrical glands excluded

to an uptake ratio of 1.3 ± 0.5 for cancer, 1.0 ± 0.5 for follicular adenomas, and 0.9 ± 0.4 for nodular goiter.

Discussion

In the preoperative diagnosis of thyroid cancer, conventional imaging techniques are clearly indicated mainly for distinguishing solitary cold nodules from multifocal nodules. The solitary nodule without demonstrable physical signs of malignancy, and without detectable radioiodine- or pertechnetate-uptake, is probably the most difficult problem in the diagnosis of thyroid cancer (Pochin 1980). Most of the cold solitary areas represent benign lesions, but the probability of malignancy is fairly high, approximately 15%–25% (Pinsky et al. 1978). In well-differentiated cancer, on the other hand, preoperative scintigraphy has demonstrated solitary cold nodules in 65% of the patients examined (Tennvall et al., to be published). If the scintigram is used as a guide for percutaneous fine-needle biopsy at cytologic examination, the possibility of adequate preoperative diagnosis is greater – but it can be very difficult to distinguish between follicular adenoma and follicular cancer even by cytology (Löwhagen and Sprenger 1974). This was also the case in the present work, where all patients were also examined with preoperative fine-needle aspiration biopsy and cytology.

Thallium-201 has currently been reported to be an excellent agent for detecting differentiated thyroid cancer, but several investigators have noted increased uptake in other thyroid lesions as well. In the present study, all but one of the differentiated carcinomas accumulated thallium-201, but the uptake ratio (C_p/C_n) does not definitely distinguish between cancer and follicular adenoma. Cervical lymph node metastases of papillary carcinoma have shown uptake of thallium, but not of technetium or iodine, as has been described earlier in a case report (Fukuchi et al. 1978). In the material presented, cystic metastases as well as other cystic lesions could not be visualized on the thallium image.

If the grossly asymmetrical glands were excluded, as illustrated in Table 3, there was a clear tendency to different uptake ratios in the malignant and the benign group. A correlation between the thallium uptake and thyroid enlargement has been described (Fukuchi et al. 1979), and we suggest that a correction for lobe size ought to be made to improve the possibilities of distinguishing between malignant and benign lesions. In the present study, the thallium image was only subjectively related to the technetium image. Improvements that are now being introduced include simultaneous double-isotope technique, by which the diagnostically interesting regions can be precisely defined and quantitatively compared, which may possibly aid in reducing the amount of errors due to lobe size. Even with the mentioned improvements, it is doubtful if uptake measurements of thallium-201 alone can distinguish between benign and malignant lesions in the individual case. However, Harada et al. (1980) have recently concluded that the thallium-201 scan is nevertheless useful for determining surgical indication. The mechanism of uptake and distribution in normal and pathological thyroid tissues is not clearly understood. Several authors have suggested that thallium has biological properties similar to those of potassium (Atkins et al. 1977; Ito et al. 1978). In an investigation in rats, Oster et al. (1978) have suggested that thallium-201 distribution reflects the cationic side of the iodine pump or possibly of blood flow. It is evident from their results that this mechanism is complex. The uptake was heavily reduced after treatment with T_3 . After treatment with TSH, there was an increased uptake, and after perchlorate decreased uptake, but these changes were not significant. In the present study the uptake of thallium-201 in the thyroid gland with an obviously normal image during thyroxine treatment, and also uptake in a lobe suppressed by an autonomous adenoma, indicate that the mechanism of thallium uptake differs from that of iodide or of pertechnetate.

Since the uptake measurements of thallium-201 could not distinguish between cancer and benign lesions, follicular adenoma in particular, the effective half-life was calculated for normal and pathological tissues. The relative disappearance rate ($\lambda_p - \lambda_n$) separated cancer from benign lesions as a group (Table 2), but not in the individual case. There is, however, much evidence for the assumption that high uptake and long half-life in relation to a normal thyroid region in the same patient indicate a well-differentiated cancer as highly probable from the clinical point of view. A low uptake or no uptake at all, on the other hand, are typical for nonmalignant tissues. It is well known that with fine-needle biopsy it can be difficult to correctly differentiate benign lesions from

differentiated thyroid cancer. Investigation with thallium-201 in addition to conventional scintigraphy can therefore be of great value for selecting patients for surgery, especially among patients who constitute a high-risk group.

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KINETICS OF ^{201}Tl UPTAKE IN ADENOMAS AND WELL-DIFFERENTIATED CARCINOMAS OF THE THYROID

A double isotope investigation with $^{99}\text{Tc}^{\text{m}}$
and ^{201}Tl

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J. RANSTAM and M. ÅKERMAN

Abstract

A visually increased uptake of ^{201}Tl chloride corresponding to a 'cold' (^{131}I or $^{99}\text{Tc}^{\text{m}}$) thyroid nodule is mostly seen in well-differentiated carcinomas but also often in follicular adenomas. Since a visually increased uptake of ^{201}Tl can be due to an increased initial uptake and/or a delayed elimination, an extended dynamic investigation was performed in patients with well-differentiated carcinomas or with follicular adenomas. Data were collected in a dynamic simultaneous double isotope ($^{99}\text{Tc}^{\text{m}}$ + ^{201}Tl) study up to 50 min after intravenous administration. Adenomas could be significantly separated from carcinomas by the elimination ($p=0.0001$), but not by the initial uptake.

The incidence of thyroid carcinomas in scintigraphic solitary 'cold' thyroid nodules (viz. with $^{99}\text{Tc}^{\text{m}}$ or ^{131}I) is usually reported as relatively high, approximately 20 per cent (2, 6). However, the high incidence of carcinoma found in solitary 'cold' nodules can often be attributed to a bias of case selection (7). To avoid this selection process and to analyse how often a carcinoma does present itself as a 'cold' nodule, the findings in the preoperative scintigraphy of 83 consecutive histopathologically confirmed thyroid carcinomas have recently been reported (12). A solitary reduced uptake was observed in 70 per cent of the entire group (in 65% of well-differentiated carcinomas) which supports the state-

ment that a solitary reduced uptake is the most frequent scintigraphic appearance of a thyroid carcinoma.

Preoperative aspiration cytology of the thyroid is not seldom inconclusive, and therefore there is a need for complementary investigations to make the preoperative diagnosis as correct as possible to reduce the number of unnecessary operations.

Evaluation of thallium scintigraphy of the thyroid has been reported by several authors. In these reports there is agreement of the general indications and findings. The aim has been to improve the preoperative diagnosis of solitary 'cold' areas in technetium or iodine scintigrams, since malignant thyroid tissues show an accumulation of thallium. The sensitivity appears to be in the order of 90–95%, while the specificity is insufficient (36–54%) to allow a distinction between benign lesions and carcinomas (4, 11, 15). In previous reports (9, 14) it was found that carcinoma as a group might have a slightly decreased disappearance rate of thallium compared with adenomas. Thus, kinetic analysis might increase the specificity.

The aim of this investigation was to further evaluate the kinetics of ^{201}Tl in order to define condi-

tions (in terms of initial uptake and disappearance rate) for optimum separation between well-differentiated carcinoma and adenoma.

Material and Methods

The criteria for inclusion in the investigation was a histopathologically confirmed well-differentiated thyroid carcinoma or a follicular adenoma with a preoperative $^{99}\text{Tc}^m$ or ^{131}I thyroid scintigram showing a solitary reduced uptake and a ^{201}Tl scintigram showing uptake in the same lesion (Fig. 1). Medullary and undifferentiated tumours have not been included in this series, because the sensitivity of preoperative aspiration cytology is high in these tumours (10, 13).

Patients with visibly reduced thallium uptake in the lesion were excluded from the study as these thallium negative lesions mostly represent benign conditions (4, 11, 15).

From August 1981 to March 1983, 33 patients fulfilled these criteria, 9 patients had a papillary thyroid carcinoma and 24 patients a follicular thyroid adenoma. The size of the smallest tumour was 18 mm in diameter.

Scintigraphic procedure. Patients were given intravenous injections of 30 MBq $^{99}\text{Tc}^m$ pertechnetate and, after a delay of 10 to 15 min, 55 MBq ^{201}Tl chloride. Data acquisition was started 6 min before the thallium injection and continued for 50 min. Data were collected by a gamma camera (Searle LFOV) equipped with a pinhole collimator and dedicated computer (Digital Equipment Corp GAMMA-11). Sequential 64×64 element images were recorded simultaneously in two channels in order to provide identical positioning for the thallium and technetium images. The kinetics was evaluated by fitting single-exponential functions, $C_{exp}(-\lambda t)$, to the background-subtracted count-density curves generated from the pathologic (p) and normal (n) regions of interest (Fig. 2). The kinetics was interpreted in terms of relative uptake (C_p/C_n) and relative disappearance rate ($\lambda_p - \lambda_n$). The clinical presentation is shown in Fig. 3.

The average curve from two regions enclosing the thyroid was used as background. This background amounted to about one third of the initial thyroid uptake, but usually did not differ significantly in the two regions, except during the injection phase. Data were fitted in the interval 6 to 44 min after injection

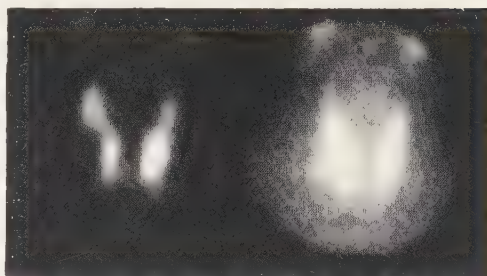


Fig. 1. Comparison between technetium and thallium scintigram in the same patient. The technetium scintigram (left) shows a defect in the caudal lateral part of the right lobe while the thallium scintigram (right) shows an uptake of thallium on the corresponding site. Histopathology revealed a papillary carcinoma measuring 25 mm in its largest diameter on this location.



Fig. 2. From the simultaneous technetium scintigram (Fig. 1, left) the pathological, normal and background areas are primarily defined for the subsequent kinetic analysis of recorded thallium uptake.

of thallium. Data were also corrected for the channel cross-talk by a first-order correction, thus:

$$(R_i)_{\text{corrected}} = R_i - (E_{ij}/E_{jj}) R_j,$$

where R_x is the count-rate in channel x , and efficiency E_{xy} the count-rate per unit activity of isotope y in channel x , as determined by phantom measurements. The efficiency ratio is of the order of 5 to 10 per cent. The cross-talk is due to scattered events from the ^{201}Tl 167 KeV and $^{99}\text{Tc}^m$ 140 keV gamma rays and to the ^{201}Tl 135 KeV gamma rays.

In the absence of this correction, the analysis of the kinetics of thallium is affected if the uptake in the nodule is compared with a normal region with high technetium uptake, the obtained relative disappearance rate ($\lambda_p - \lambda_n$) being incorrectly increased by the order of 0.01 min^{-1} .

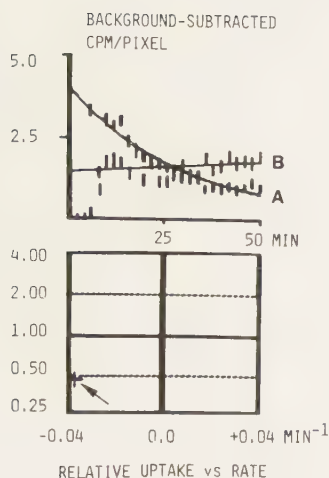


Fig. 3. Example of kinetics of thyroid ^{201}Tl uptake for the same patient as in Figs 1 and 2. Above: Elimination curves in normal (A) and cancerous tissue (B). The areas below the curves are directly proportional to the visual thyroidal scintigraphic uptake of thallium. Below: Diagram showing the extrapolated zero-times uptake ratio $\ln(C_p/C_n)$ and relative disappearance rate $(\lambda_p - \lambda_n)$. The current values show a decreased initial uptake but a delayed elimination.

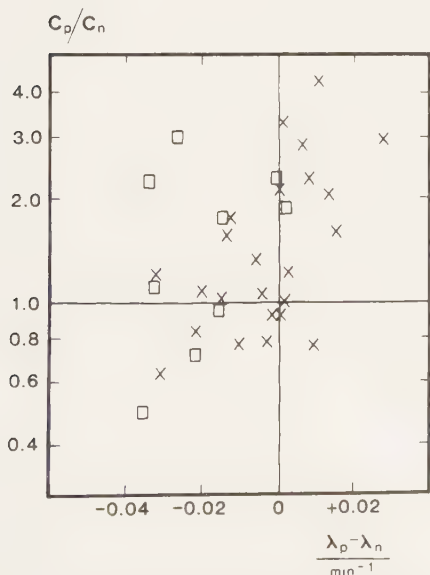


Fig. 4. The extrapolated zero-time uptake ratio $\ln(C_p/C_n)$ vs relative disappearance rate $(\lambda_p - \lambda_n)$ in 24 patients with follicular adenomas (x) and in 9 patients with papillary carcinomas (□).

Results

The initial thallium uptake ratio $\ln(C_p/C_n)$ and relative disappearance rate $(\lambda_p - \lambda_n)$ for all 33 patients are presented in Fig. 4. The carcinomas occupy the left half of the diagram, indicating lower disappearance rates, whereas there is no obvious separation in initial uptake values between carcinomas and follicular adenomas.

The mean value of the disappearance rates for carcinoma and adenoma were -0.021 (SD 0.014) min^{-1} and -0.003 (SD 0.015) min^{-1} respectively ($p < 0.01$). The corresponding values for the uptake ratio were 0.316 (SD 0.598) and 0.317 (SD 0.522), respectively.

The present measurements have been pooled with corresponding data from a previously reported series of 36 patients with solitary 'cold' thyroid nodules in conventional scintigraphy, subject to a dynamic ^{201}Tl examination. Out of these patients, 24 fulfilled the criteria for inclusion in the present series (14). The pooled data are presented in Fig. 5.

Discriminant analysis of adenomas and carcinomas of the pooled material in respect to the disappearance rate and the uptake showed that the disappearance rate could be used to separate the two groups statistically ($p = 0.0001$). The optimum value for discrimination was found to be at a disappearance rate of -0.01 min^{-1} .

The uptake was a poor discriminator ($p = 0.45$). There was no interaction between the two rates ($p = 0.86$).

All p-values have been calculated by F-tests and multivariate F-tests (16).

Testing the optimum value for discrimination from the clinical point of view (Fig. 5) a vertical line, drawn at a value of -0.01 min^{-1} divides the patient material in a high-risk group (11/23 patients with carcinomas) to the left and a low-risk group (5/34 patients with carcinomas) to the right.

Discussion

When complementary thallium scintigraphy is performed in patients with solitary 'cold' nodules (viz. with $^{99}\text{Tc}^m$ or ^{131}I) a visually reduced uptake of thallium corresponding to the examined nodule mostly represents a benign lesion. On the other hand, a visually increased uptake is mostly found in well-differentiated thyroid carcinomas of papillary and follicular types but also often in benign thyroid adenomas (4, 11, 15).

In a previous report (14) the elimination of thallium was found to be generally delayed for different types of pathologic tissues. In these tissues thyroid carcinoma as a group was distinguished from various benign lesions by a lower disappearance rate. Among the benign disorders a delayed elimination of thallium was most marked for follicular adenomas.

In the present investigation the difference in rate of elimination between well-differentiated carcinomas and adenomas was evaluated for clinical use in the differential diagnosis.

It is apparent from Figs 4 and 5, that the initial uptake values of thallium alone are of no value for differentiation between benign and malignant lesions. However, it is possible to obtain a good separation between follicular adenomas and well-differentiated carcinomas by an analysis of thallium elimination. In our data, this differentiation could not be improved by using both parameters in conjunction.

Thus, it was possible (Fig. 5), to divide the patients with a visual thallium uptake in a high-risk group (48% carcinomas) and a low-risk group (15% carcinomas). The possibility of defining a high-risk group of patients having a carcinoma is of value in the process of surgical decision making.

The mechanism of thallium accumulation *in vivo* is not fully understood neither in malignant cells nor in normal cells. The disappearance of thallium from blood is extremely rapid and intracellular deposition is nearly immediate (1, 5). Therefore the concentration of thallium in the thyroid is related to factors besides blood flow.

Since the thallium uptake in the thyroid gland is ouabain sensitive (18), parts of the thallium uptake is mediated by Na-K-ATPase, where potassium is replaced by thallium (3, 8). This conclusion is also supported by the analogous biological distribution of thallium and potassium (5). Since the behaviour of thallium is related, but not identical, to that of potassium, the thallium accumulation is certainly to some extent an expression of tissue cellularity. This is in agreement with the observations that follicular adenomas with low or absent uptake of thallium are usually cystic, saturated with colloid or showing signs of bleeding, while follicular adenomas with increased thallium uptake usually belong to the microfollicular or the Azkanazy-cell group (9, 14).

VENUTA *et coll.* (17) have shown in *in vitro* studies on transformed thyroid cells that the increased

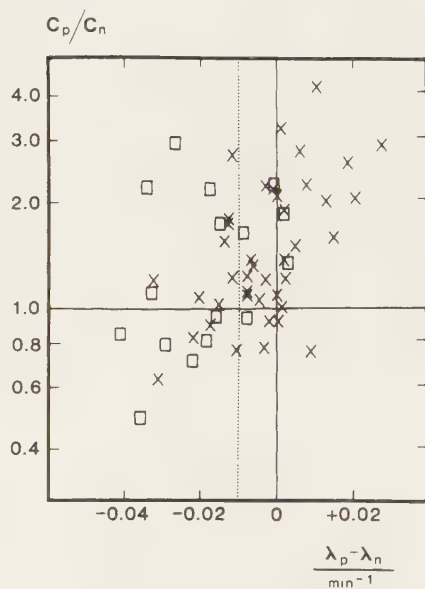


Fig. 5. Present data (as in Fig. 4) combined with corresponding data from a previous report (14). Optimum discrimination between benign and malignant diseases was obtained at a value of -0.01 min^{-1} (dashed line) which divides the patient material in a high-risk group (11/23 patients with carcinomas) to the left and a low-risk group (5/34 patients with carcinomas) to the right.

uptake of thallium may be related to both cell transformation and to growth rate.

To our knowledge, no special study of the elimination of thallium from thyroid cells has been published.

The present kinetic analysis of ^{201}Tl demonstrated that a delayed elimination of the isotope from a thyroid lesion might indicate a malignant thyroid tumour. This finding is important in preoperative investigation when fine needle aspiration biopsy only has given a picture of a follicular neoplasm.

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STUDIES OF NMR-RELAXATION-TIMES IN MALIGNANT TUMOURS AND NORMAL TISSUES OF THE HUMAN THYROID GLAND

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INTRODUCTION

The importance of NMR besides providing tomographic images is its potential for analysing physiological and pathophysiological changes by measuring the spin relaxation times, T1 and T2. We have considered thyroid gland as a suitable model for these studies.

The preoperative investigation of patients with palpable nodule in the thyroid is still insufficient. Thus, a solitary area in a thyroid scintigram which shows no evidence of uptake of iodine or technetium pertechnetate represents a carcinoma until proven otherwise. This general rule is not acceptable since a cold area is usually produced by a benign lesion. Preoperative aspiration biopsy cytology of the thyroid is not seldom inconclusive. Therefore, there is still a need for complementary methods to differentiate between benign and malignant lesions. We have studied the feasibility of NMR-relaxation-times in this respect (1). Only a few NMR-measurements of thyroid gland tissue have up to now been reported (2,3,4). Those measurements have been performed on samples from thyroid tissues in vitro at a temperature below the body temperature. However, only one of these reports (2) evaluate both T1- and T2-values on human thyroid tissues, including two carcinomas.

MATERIAL AND METHODS

Fourteen specimens from 6 patients have been investigated; 2 patients with papillary carcinoma, 4 patients with a benign lesion corresponding to a scintigraphically cold area. Specimens have been taken from the suspected lesion and from macroscopically normal tissue for each patient.

The NMR-measurements have been performed for protons at a frequency of 10.7 MHz with the pulse sequences: $(90^\circ - \tau - 90^\circ)$ and $(90^\circ - \tau - 180^\circ - \tau)$ for T1 and T2 respectively. The NMR-measurements have been done at 37°C on fresh extirpated samples (0.5-3.2 g) from thyroid lobes. The results of the relaxation-time-measurements have been correlated to a quantitative histopathologic examination, viz. the proportions of colloid, fibrosis, necrosis and hemorrhage in benign and cancerous tissue have been estimated (Fig 1 and Table I). No specimen showed a mixture of benign and malignant thyroid cells.

Furthermore correlations to total water content have been performed in eleven samples.

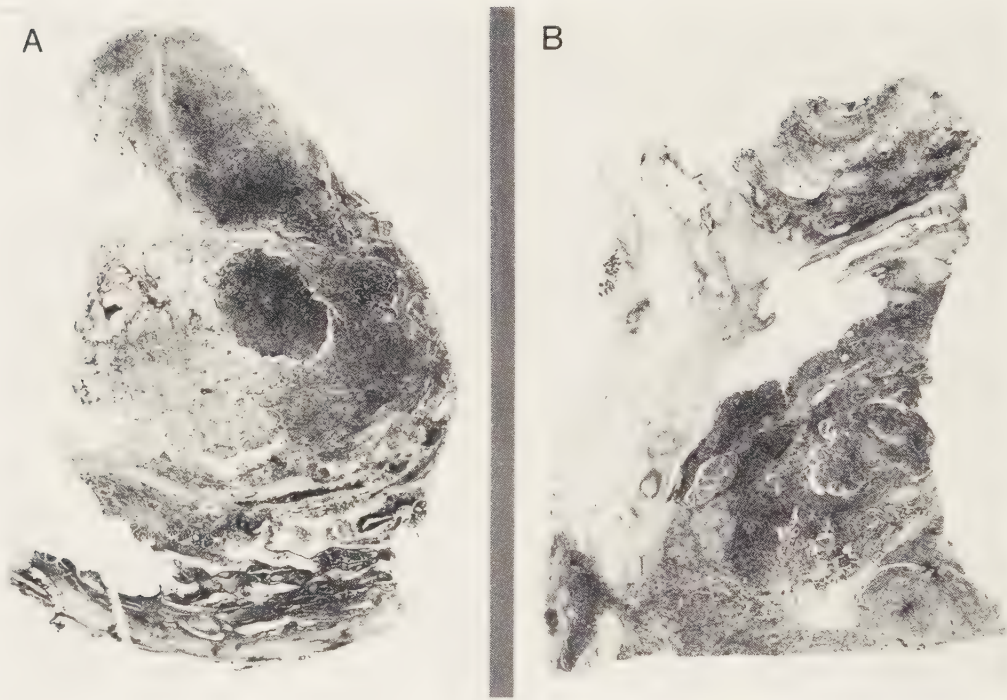


Figure 1. Two samples from different parts of the same tumour. A. Small amount of fibrosis (+). B. Considerable amount of fibrosis (++).

TABLE I. Estimated proportions of different tissue components at histologic examination of 14 samples studied in vitro.

	Normal tissue or benign lesion (n=10)				Carcinoma (n=4)			
	0	+	++	+++	0	+	++	+++
Fibrosis	5	5				3	1	
Colloid			1	9	4			
Necrosis	10				4			
Hemorrhage	10				4			

RESULTS

The T1- and T2-values of malignant and benign tissues ranged between 419-721 ms and 47-96 ms respectively. Both rate constants varied in direct proportion to water content.

Three out of four specimens with papillary thyroid carcinomas had the same proportion of colloid and fibrous tissue. They had a narrow range of T1- and T2-values; the T1-values varied between 617-643 ms (Fig 2a) and T2-values between 70-82 ms (Fig 2b). One sample with papillary carcinoma differed from the others in respect to having a greater proportion of fibrous tissue. Both rate constants were shorter for this tumour (T1 = 491 ms and T2 = 57 ms).

For the ten specimens from benign lesions the T1-values varied between 419-721 ms and T2-values between 47-96 ms.

With increasing proportion of colloid a tendency towards shorter T1- and T2-values was observed (Fig 3).

Neither the samples with carcinomas nor those with benign histology revealed necrosis, hemorrhage or oedema.

DISCUSSION

The results of NMR-relaxation-times in the present study performed on samples from human thyroid at 37°C may indicate a possibility to discern the effects caused by different proportions of tissue i.e. fibrosis and those resulting from true changes related to malignant growth.

Schara et coll. (4) tested the applicability of T1-measurements at a frequency of 32 MHz and room temperature for the characterization of malignant tissues in human thyroid gland. Values exceeding 700 ms, apart from necrotic tissue, were found to be characteristic for thyroid cancer (including moderately differentiated follicular carcinomas). Only well differentiated papillary carcinomas showed T1-values below this level. It was therefore assumed that the degree of the tumour differentiation was correlated to T1. Sinadinović et coll. (3) found, however, in rat thyroid glands a correlation between increased NMR-relaxation-times and concomitant morphologic changes induced by antithyroid substances (i.e. decreased colloid content).

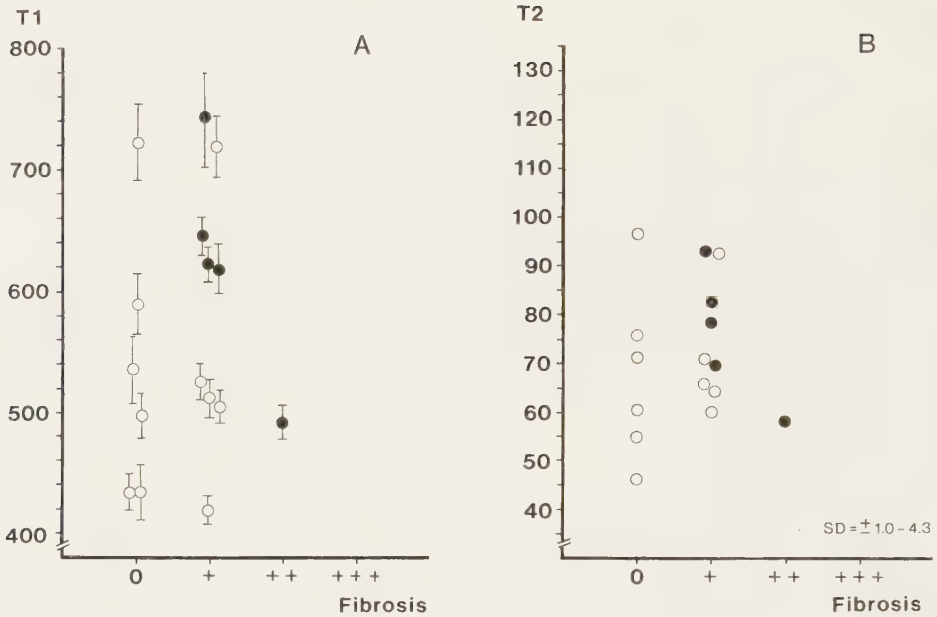


Figure 2. The relation between T1-values (A) and T2-values (B) and the degree of fibrosis. Three out of four samples with papillary carcinoma had the same proportions of fibrous tissue (and colloid). They had a narrow range of T1- and T2-values. One sample had a greater proportion of fibrous tissue. Both T1- and T2-values were shorter for this tumour (● indicates carcinoma and O benign lesion).

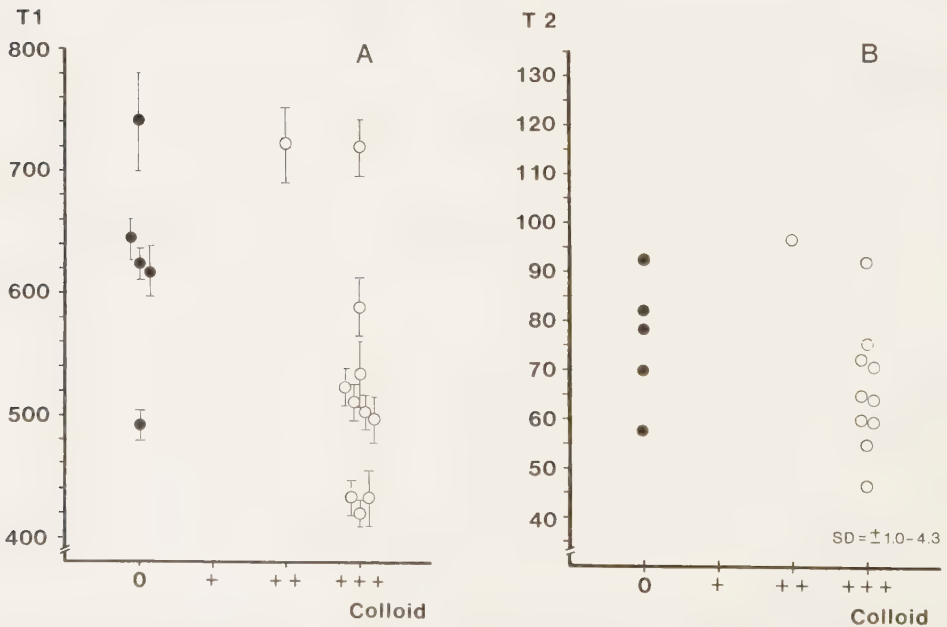


Figure 3. The relation between T1-values (A) and T2-values (B) and the degree of colloid. With increasing proportion of colloid a tendency towards shorter T1- and T2-values may be observed (● indicates carcinoma and O benign lesion).

The observations of different relaxation-times for colloid, fibrous tissue and malignant tissue may be an expression of varying fractions of different water phases (5). Therefore, it is necessary to continue studies to evaluate NMR-relaxation-times in discriminating thyroid cancer from benign lesions.

In addition, possible circulation-induced effects on the NMR-relaxation-times must be taken into consideration.

SUMMARY

NMR-measurements on human thyroid tissues in vitro have been performed for protons at a frequency of 10.7 MHz with the pulse sequences: $(90^\circ - \tau - 90^\circ)$ and $(90^\circ - \tau - 180^\circ - \tau)$ for T1 and T2 respectively. The measurements have been done at 37°C on fresh extirpated samples from thyroid lobes.

A total of 14 specimens from two patients with papillary carcinomas and 4 patients with adenomas have been investigated.

Three out of four specimens with papillary thyroid carcinomas had a narrow range of T1- and T2-values; the T1-values varied between 617-643 ms and T2-values between 70-82 ms.

For the ten specimens from benign lesions the T1-values varied between 419-721 ms and T2-values between 47-96 ms.

Further investigations are needed before any evaluation can be done of the applicability of NMR-relaxation-times as a complementary method in pre-operative assessment of 'cold' thyroid nodules.

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IS THE EORTC-PROGNOSTIC INDEX
OF THYROID CANCER VALID IN
DIFFERENTIATED THYROID CARCINOMA?

Retrospective Multivariate Analysis
of Differentiated Thyroid Carcinoma
with Long Follow-up

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ABSTRACT

The EORTC Thyroid Cancer Cooperative group presented in 1979 a prognostic index including all histologic groups of thyroid carcinomas based on a multivariate analysis on 507 patients with a median follow-up of 40 months.

The purpose of the present report is not only to test with a multivariate analysis the validity and reproducibility of this index upon a patient material consisting of 226 differentiated thyroid carcinomas with a considerably longer follow-up (11 years), but also to test possible prognostic factors other than those proposed by EORTC. In contrast to the EORTC study, neither sex nor age at diagnosis, when deaths in intercurrent disease were taken into account, were found to be of major importance. The only two variables included in this index, which could be reproduced as important were locally advanced disease and distant metastases. When testing other variables, marked cellular atypia proved to be an important predictor.

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INTRODUCTION

A number of parameters have been considered to be of prognostic importance to predict survival for patients with differentiated thyroid carcinoma, e.g. age at diagnosis, sex, histopathology, extent of primary tumour, lymph node involvement and the presence of distant metastases (1-5). There is, however, little agreement on the relative importance of the various clinical and morphological variables.

Due to the multiplicity of prognostic factors and their interdependence it is necessary to make a prognostic assessment with a multivariate analysis which separates the effects of the variables. At present there are only two reports in which this method has been employed (6, 7). The EORTC Cooperative Group has studied the relative prognostic significance of age, sex, cell-type, clinical extent of tumour, lymph node involvement and presence of distant metastases. However the EORTC study comprises all histologic types of thyroid carcinoma and the median follow up is rather short (40 months). Several authors have stressed that late recurrence of differentiated thyroid carcinomas is not unusual and therefore advocated a long follow-up (3, 8, 9).

The purpose of the present study was to test the EORTC prognostic index on a patient material consisting solely of differentiated thyroid carcinomas with a considerably longer median follow up (11 years). In addition, two other analyses were performed, one dealing with pretherapeutic clinical factors only and the other concerning histopathological parameters in combination with age and sex. The purpose of these two additional studies was to investigate if any important prognostic factors other than those proposed by the EORTC Cooperative Group could be identified.

MATERIALS AND METHODS

Patient material

The mean annual incidence of thyroid carcinoma in the region served by the hospital was 33 (range 22-45) during the period (Cancer Incidence in Sweden 1958-1972). The corresponding figure for well-differentiated thyroid carcinoma (viz: papillary and follicular carcinomas) was 25 (range 19-34). During the period there was a slight increase in incidence.

During a period of 18 years (1955-1972), a total of 262 patients with histopathologically verified differentiated thyroid carcinomas, i.e. papillary, follicular and medullary (10) were referred to the Department of Oncology, University Hospital, Lund. These groups constituted 74 per cent of the total number of patients with thyroid carcinomas. Follow-up was concluded in May, 1981.

For the present analysis the median follow-up time was 11 years, but 26% of the patients have been followed at least 15 years, justifying the construction of survival curves up to 15 years.

Histopathologic examinations

All microscopic slides were re-examined by one investigator (MA), and tumours were grouped according to the WHO classification (10). Re-examination was performed on the original slides. When these were found to be of technically inferior quality, new slides were prepared from existing tissue blocks. The pathologist had no knowledge of the clinical course.

Anaplastic tumours containing follicular or papillary structures were considered to be anaplastic carcinomas and therefore these were not included in the present study.

The diagnosis of follicular carcinoma was established if evidence of invasion was found, either into the capsule, into blood vessels or into adjacent thyroid tissue, if it did not contain papillary structures. These criteria have recently been carefully described by Kahn and Perzin (11).

EORTC has interpreted follicular carcinomas showing a trabecular pattern (i.e. solid tumours) as less-differentiated tumours and the others as well-differentiated (12). We have, however, studied two aspects of the differentiation of follicular carcinomas, growth pattern of the tumour and presence of marked cell atypia. Follicular carcinomas were divided into two groups according to growth pattern: encapsulated carcinomas and tumours without capsule growing diffusely into thyroid parenchyma.

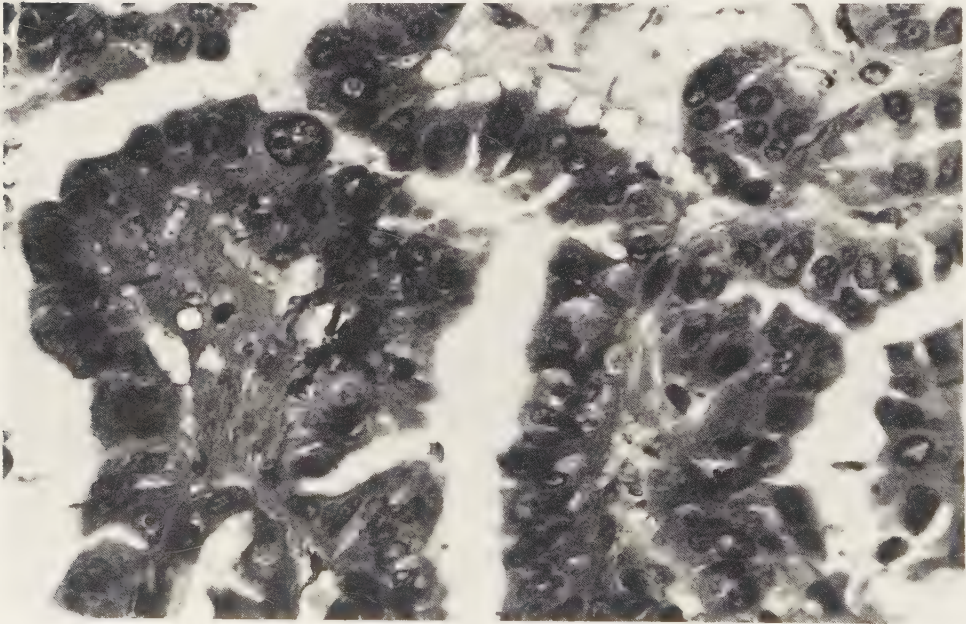


Figure 1. Marked cellular atypia in a papillary carcinoma. The papillae are covered with cells of varying size and with polymorph nuclei. Here and there prominent nucleoli. No ground glass nuclei. HEx400. Compare with Fig. 7a in reference 5.

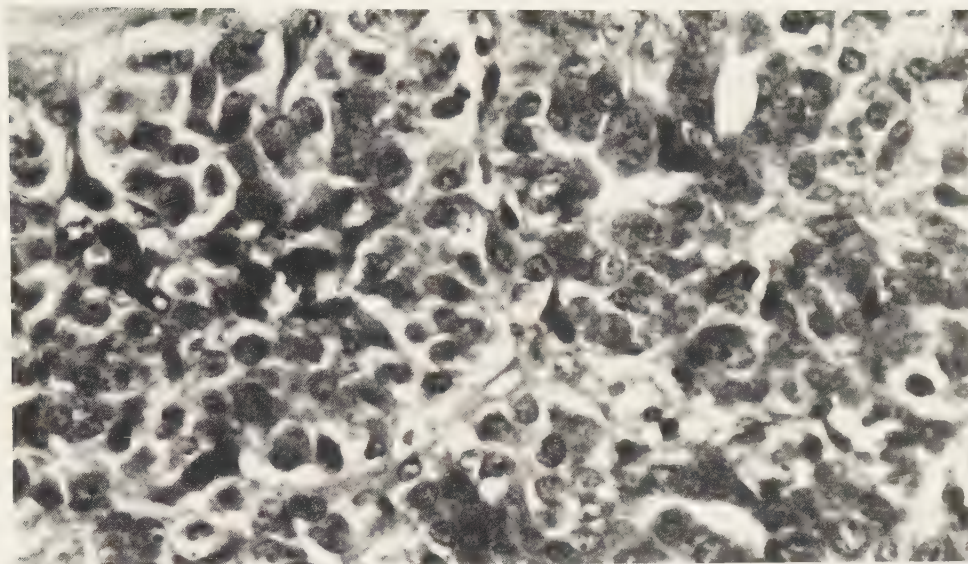


Figure 2. Marked cellular atypia in a follicular carcinoma. Only a few recognizable follicles, but principally solid structures (trabecular carcinoma according to EORTC). Nuclei are polymorphic with prominent nucleoli. HE x 400

Marked cellular atypia (MCA) (Figs 1 and 2), was found at re-examination in six (4 %) of the papillary carcinomas, in fourteen (26 %) of the follicular carcinomas (7/30 encapsulated and 7/23 non-encapsulated), and in three (12 %) of the medullary carcinomas.

Occult carcinoma (≤ 10 mm) were found in 29 patients. Eleven of these tumours were diagnosed due to lymph node metastases.

Excluded from further analysis were seven patients reclassified as having benign tumours, and 29 patients whose microscopic slides could not be found for re-examination (Table 1). The excluded patients with verified malignant tumours did not differ from the entire group with respect to age, sex ratio, or survival.

TABLE I. Distribution of histologic types re-examined and not re-examined specimens of 262 patients.

Histologic type	Specimen re-examined	Specimen not re-examined
Benign	7	-
Papillary carcinoma	143	19
Follicular carcinoma	57	10
Medullary carcinoma	26	-
Total	233	29

A total of 226 patients (86 %) thus fulfilled the criteria and form the basis for the following studies:

- Analysis A: Testing the validity and reproducibility of the EORTC prognostic index;
- Analysis B: Testing the influence of pretherapeutic-clinical factors on survival;
- Analysis C: Testing postsurgical (histopathological) tumour factors in combination with the patient factors: age at diagnosis and sex (221 patients).

Analysed factors

The variables, which are analysed in the three multivariate studies, i.e. the prognostic factors proposed by EORTC and the additional factors studied, are presented in Tables II and III.

Fifty-six patients were male, with a median age of 48 years, and 170 were female, with a median age of 49 years. The median age in the total patient material irrespective of sex was 49 years (range 8 - 83).

The clinical assessment of extent of the primary tumour was classified as T0, T1, T2 or T3 lesions according to UICC, 1968 (13). The extent of tumour was also classified according to AJCCS, 1967 (14). These classification systems are not quite compatible; T3 tumours according to UICC can best be interpreted as a combination of T2 and T3 tumours according to AJCCS (tumour diameter exceeding 5 cm or tumour fixed to adjacent structures, respectively). Therefore, tumours classified according to AJCCS were pooled in two groups: T0 with T1, and T2 with T3. The feasibility of this pooling was confirmed by survival curves for T2 and T3 tumours significantly differing from those for T0 and T1 tumours ($p < 0.0001$).

The histopathological assessment of extent of primary tumour was constructed in accordance with UICC, 1978 (15). The concept pT was further split up into two co-variables: size of the tumour (≤ 1 cm or > 1 cm) and tumour invasion beyond thyroid capsule (pT4) or not.

The results of cytology have not been taken into consideration as fine needle aspiration cytology was only routinely performed during the last years of the study-period.

Regional lymph node involvement as judged at the clinical examination was classified as N+ (Table III). At operation, seven out of 59 patients (12%) with N+ showed a benign histopathology. Histopathologically verified metastases in regional lymph nodes irrespective of clinical findings have been designated as pN+. In 14 patients, lymph node metastases (of these 12 papillary carcinomas) showed extranodal growth (pN3, UICC 1978). In several patients who were not sufficiently surgically explored, lymph node status could not be assessed, and these cases have been designated pNx. The factor N+ was evaluated in analyses A and B. To study pN+ in analysis C, it was necessary to pool pNx with pN-.

Distant metastases were found in a few patients at diagnosis and in most of these cases in multiple sites. Therefore, in contrast to the EORTC group, distant metastases were not di-

vided into two variables depending on whether only one or several metastatic sites were involved.

In the multivariate analyses B and C, no factor was omitted a priori, although some of the factors did not seem to be of importance for survival in univariate analysis (since one factor can be confounded by others in such an analysis).

As in the EORTC study the therapy has not been taken into account in the analysis of survival because of the complexity and continually changing policy of treatment.

Statistical methods

Survival was estimated by the actuarial method. Differences in cumulative survival between groups was tested by the Lee-Desu test (16).

Prognostic factors were assessed multivariately by Cox's proportional hazards model (17; Appendix 2).

Bivariate correlation between covariates was evaluated by Pearson's correlation coefficient. All p-values are two-tailed and p-values less than 5 % are referred to as significant.

Comparisons were made with national life-table figures representative for a Swedish population with the same age and sex distribution as the investigated group of patients in order to estimate death in intercurrent disease (18).

The calculations were made by the statistical packages SPSS and BMDP on a VAX 11/780 computer.

RESULTS

Characteristics of single variables

The prognostic variables for survival used to identify risk groups proposed by the EORTC cooperative group are presented in Table II. This table also gives the number of patients, deaths, total months of follow-up and death rate (expressed as deaths per 1000 patient months) for each variable divided on levels identical to the EORTC-study. Also the variables included in analysis B are presented in this table.

The set of proposed additional parameters is presented in the same way in Table III. These factors form, together with the EORTC-prognostic factors of the EORTC study, the basis for analysis C.

Pair-wise correlations between prognostic variables

Correlations were calculated between age at diagnosis, sex, follicular carcinoma growing diffusely into thyroid parenchyma (FCD), T-category according to AJCCS (1967), lymph node involvement (N+), distant metastases, non-occult tumour, histological verification of tumour growth beyond thyroid capsule (pT4) and marked cellular atypia (MCA). The pair-wise correlations between these variables are presented in Table IV.

The clinical assessment of the extension of primary tumour expressed as T2 + T3 (AJCCS, 1967) showed a significant correlation to the histopathological verification of tumour growth beyond thyroid capsule (pT4, UICC, 1978) ($p < 0.0005$), thus indicating a good correspondence between the two classification systems.

TABLE II. Prognostic variables as proposed by EORTC (above the dashed line) and additional clinical variables (below the dashed line) for 226 patients with differentiated thyroid carcinoma.

Variable	Analysis	Levels	No. of patients	No. of deaths	Total follow-up months	Death rate*
Age	A, B**	0-30 31-40 41-50 51-60 61-70 71-	37 39 39 39 45 27	3 - 5 16 24 25	5 484 7 080 6 144 4 164 5 256 1 968	0.55 - 0.81 3.84 4.57 12.70
Sex	A, B	Male Female	56 170	22 51	7 056 23 040	3.12 2.21
Histologic type	A	MEC/FCD*** All other	49 177	21 49	5 904 24 192	3.56 2.03
T-category (UICC 1966)	A	T0 T1 T2 T3	216 10	65 8	29 544 552	2.20 14.49
Metastases	A, B	M0 M1	216 10	65 8	29 304 792	2.22 10.10
T-category (AJCC 1967)	(A), B	T0 T1 T2 T3	179 47	43 30	25 584 4 512	1.68 6.65
Lymph node involvement (clinical assessment)	B	N1 N2 N3 N0	59 167	19 54	7 500 22 596	2.53 2.39
Total			226	73	30 096	2.43

* Death rate expressed in deaths/1 000 patient months

** A=Variables included in the analysis testing the validity and reproducibility of the EORTC prognostic index; B=Variables included in the analysis testing the influence of pretherapeutic clinical factors on survival.

*** MEC and FCD stand for medullary carcinoma and diffusely growing non-encapsulated follicular carcinoma, respectively.

TABLE III. Additional investigated postsurgical variables in 221 patients with differentiated thyroid carcinomas.

Variable	Levels	No. of patients	No. of deaths	Total follow-up months	Death rate*
pT4**	No	167	37	24 648	1.50
	Yes	54	32	5 028	6.36
Tumours size	>10 mm	192	62	25 512	2.43
	≤10 mm	29	7	4 164	1.68
Regional lymph node involvement	N0pN-**	44	9	5 712	1.58
	N1pN-	7	2	972	2.06
	N1pN1	46	13	5 904	2.20
	N0pN1	28	7	3 912	1.79
	N0pNx	91	34	2 792	2.66
	N1pNx	5	4	384	10.91
Marked cellular atypia	No	198	54	27 708	1.95
	Yes	23	15	1 968	7.62
Total		221	69	29 676	2.33

* Death rate expressed in deaths/1 000 patient months

** pT4, pN according to UICC 1978.

In addition, as shown in Table IV, significant correlations were found between the following variables:

- (1) increasing age at diagnosis and locally advanced tumour (T2+T3) or tumour invasion beyond thyroid capsule (pT4);
- (2) T2+T3 as well as pT4 and marked cellular atypia (MCA);
- (3) distant metastases and MCA;
- (4) lymph node involvement (N+) correlated significantly to pT4 as well as to male sex but showed a negative correlation to age at diagnosis;
- (5) FCD was significantly correlated to distant metastases, T2+T3, pT4 and MCA.

TABLE IV. Pairwise correlation between prognostic factors of differentiated thyroid carcinomas. (p-values are given within brackets).

	Age	Male sex	>10 mm	T2+T3	pT4	N+	M+	FCD	MEC	MCA
Age	-									
Male sex	-0.073 (0.137)	-								
Non-occult tumour (>10 mm)	-0.0001 (0.499)	-0.029 (0.337)	-							
Locally advanced tumour (T2+T3, AJCCS 1967)	0.286 (<0.0005)	0.006 (0.466)	0.003 (0.484)	-						
Tumour growth invading beyond thyroid capsule (pT4)	0.227 (<0.0005)	0.069 (0.154)	0.127 (0.029)	0.289 (<0.0005)	-					
Lymph node involvement (N+)	-0.255 (<0.0005)	0.121 (0.034)	-0.042 (0.267)	-0.048 (0.235)	0.219 (0.001)	-				
Presence of distant metastases (M+)	0.076 (0.129)	-0.024 (0.361)	0.059 (0.191)	0.021 (0.377)	0.055 (0.207)	-0.015 (0.411)	-			
Follicular cancer diffusely growing (FCD)	0.086 (0.101)	-0.053 (0.214)	0.089 (0.095)	0.138 (0.020)	0.186 (0.003)	-0.068 (0.155)	0.252 (<0.0005)	-		
Medullary carcinoma (MEC)	-0.021 (0.378)	0.188 (0.003)	0.101 (0.070)	-0.040 (0.277)	-0.017 (0.400)	0.059 (0.193)	-0.076 (0.131)	-	-	
Marked cellular atypia (MCA)	0.094 (0.081)	0.045 (0.250)	0.0008 (0.495)	0.209 (0.020)	0.255 (<0.0005)	0.090 (0.092)	0.108 (0.054)	0.224 (<0.0005)	0.011 (0.435)	-

- = Inverse correlation

Multivariate analyses

Analysis A (Table V A) shows the outcome of Cox proportional hazard model applied to the prognostic factors proposed by the EORTC cooperative group. The significant negative prognostic variables for survival were found to be in order of relative risk: age at diagnosis, distant metastases and the extent of primary tumour. Sex, medullary carcinoma or FCD were not proven to influence the survival. Changing the classification of T-category (viz: T3-tumour according to UICC replaced by T2 + T3 according to AJCCS, as described earlier) did not alter the findings.

TABLE V. Significant negative prognostic variables for survival of differentiated thyroid carcinomas.

A. Applying the prognostic variables of EORTC.

B. Applying only pretreatment variables including age and sex.

C. Applying postsurgical variables in combination with age and sex.

Negative prognostic factors	Relative risk	Coefficient*	p-value	Occurrence
A. Age at diagnosis	5.98**	0.0708	<0.00005	
Distant metastases	3.82	1.3409	0.0050	4.4 %
T3 (UICC 1966)	3.68	1.3035	0.0042	4.4 %
B. Age at diagnosis	6.14**	0.0726	<0.00005	
Distant metastases	4.22	0.4393	0.0023	4.4 %
T2 + T3 (AJCCS 1967)	2.25	0.8119	0.0019	20.7 %
Lymph node involvement (according to clinical assessment)	2.14	0.7646	0.0106	26.1 %
C. Age at diagnosis	6.36**	0.0740	<0.00005	
Marked cellular atypia	3.85	1.3468	0.0002	10.4 %
pT4 (UICC 1978)	2.13	0.7574	0.0063	24.4 %

* Coefficient (=B'; Appendix 2) for survival function.

** A death-risk ratio between a person 65 years and one 40 years of age at diagnosis.

Analysis B (Table V B) indicates that high age is the most important prognostic factor. Presence of distant metastases, advanced T-stage and lymph node involvement in falling order of relative risk were found to be of prognostic value. Neither in this study was sex found to be a prognostic factor of importance.

In analysis C (Table V C), the significant prognostic variables were found to be in falling order of relative risk: age at diagnosis, MCA and tumour invasion beyond thyroid capsule.

Estimation of deaths in intercurrent disease

Since the group of operated patients entered the study at admission to the Department of Oncology for additional therapy or for follow-up, no deaths from surgical complications were encountered. There were neither any deaths from treatment complications nor any over-representation of deaths from other malignant diseases. The area between the two curves in Fig 3 therefore represents deaths in differentiated thyroid carcinoma during a follow-up time of 15 years. This illustrates that the prognosis of differentiated thyroid carcinomas is good, the survival curves differing with 8.2 %, 11.7 % and 9.7 % at five, ten and fifteen years after diagnosis respectively.

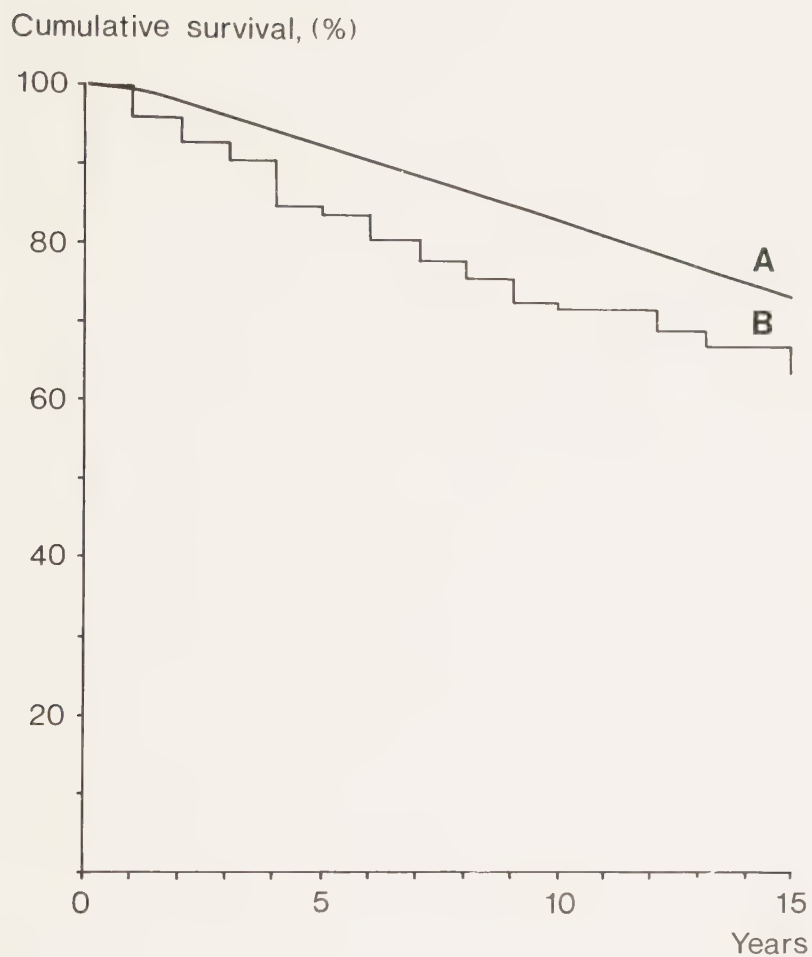


Figure 3. Survival of 226 patients with differentiated thyroid carcinomas (B) compared to survival in an age- and sex-matched Swedish population (A). The area between the two curves indicates death from differentiated thyroid carcinoma.

DISCUSSION

The EORTC Thyroid Cancer Cooperative Group presented in 1979 a prognostic index for thyroid carcinomas based on a multivariate analysis using a Weibull survival model on 507 patients originating from 23 various European hospitals and with a median follow-up of 40 months (Appendix 1).

It was proposed that this prognostic index could be used to predict survival for individual patients, as an adjustment variable in treatment comparison or as a stratification variable in designing prospective randomized trials of treatment (6).

Ladurner et al (19) compared the EORTC prognostic variables with the clinical course of 169 follicular carcinomas with a median follow-up of 6.6 years. However, the prognostic factors were only evaluated in monofactorial tests. In contrast to the EORTC study the importance of age or sex could not be confirmed. Factors associated with a significant decrease in survival rates were extrathyroidal disease, distant metastases, lymph node involvement and widely invasive (follicular) carcinomas.

Thus, a multitude of prognostic factors have been demonstrated as important predictors of survival for thyroid carcinoma, especially for differentiated thyroid carcinoma. As seen in Table IV strong correlations exist between several of them. Therefore, in an investigation of a predictor with monofactorial analysis, as presented in Table II, the results are most likely biased by the distribution of the study population among the other factors, and are thereby dependant on the study-design.

This is possibly the primary cause for the conflicting results of various reports on prognostic factors in thyroid carcinoma. Only in two studies have the prognostic variables been determined by multivariate analysis, which implies simultaneous control of investigated variables with potential prognostic value.

The patients in the EORTC study represented all histologic types of thyroid carcinomas, including anaplastic giant cell carcinoma. Since this particular type of tumour is associated with an extremely poor prognosis, a late onset and a relatively high proportion of men (20) will thus introduce a greater heterogeneity.

Warnebo et al (7) reported on a multivariate regression analysis of 157 well-differentiated carcinomas with a longer median follow-up time treated at the University of Virginia. Investigated prognostic factors were: age at diagnosis, sex, stage, histological type and type of operation. It was found in order of priority that only stage, age and histologic type had significant impact on survival. Distant and nodal metastases and the extent of the primary lesion were not analysed as separate variables, but in combination with each other. Depending on the postsurgical extent of the primary lesion (according to a modification of AJCCS, 1978) and the presence or absence of nodal and distant metastasis the patients have been divided into four stages. Therefore the relative importance of these variables cannot be compared with the EORTC study and the present study. The type of multivariate analysis applied was not specified.

In a recently published report by one of the authors of the EORTC report, (6) a comparison was made between Cox and Weibull models with covariates applied on different patient materials, among them the thyroid cancer material of EORTC. The results of the Weibull model applied to this material after removing a single outlier were markedly different from the original results. On the other hand, the two fits for the Cox model were similar and were not affected by the outlying survival time. This means that care is required in fitting and interpreting parametric models. In other respects, however, the two multivariate analytic models were regarded as equivalent.

Treatment was not studied either in the EORTC report or in the present report because both the indications for, and the types of therapy have been changing. In the American study of

well-differentiated thyroid carcinomas, the type of operation was evaluated, viz: comparing lobectomy/partial lobectomy with total/ subtotal thyroidectomy. This difference in surgical treatment was not found to have a significant impact on survival. Since therapy has not been included in the analysis, we can not rule out the possibility that therapy, if taken into account, might alter the importance of some prognostic factors.

Sex

In contrast to the EORTC study, sex was not found to be of prognostic importance. Females tended to have a slightly better outcome than men, but this was not significant.

These observations are in agreement with the findings of Warnebo et al (7). Franssila (22) found only weak evidence that prognosis varied with sex. Other authors have stressed the importance of sex as one of the major determinants to survival in differentiated thyroid carcinoma (2, 23, 24). In these reports sex has been studied as an independent variable without considering covariations with other prognostic factors.

The findings of EORTC might be explained by the fact that undifferentiated thyroid carcinomas have been included in the study, since they have another sex ratio compared to differentiated carcinomas (20).

Age at diagnosis

Age at diagnosis was found to be the most important prognostic variable. The risk of dying was directly proportional to the age of the patient. This finding is in agreement with that of EORTC. The importance of age for the prognosis has also been emphasized in many other reports (2, 4, 23).

The variable age at diagnosis was both in the present analysis A and in the EORTC study not adjusted for death in intercurrent disease. The results of the present three analyses (Table V A-C) revealed an approximately six-fold (6.0-6.4) risk to die for a person aged 65 at diagnosis compared to a person aged 40 at diagnosis. However, according to statistics based on Swedish national life-tables (1970), the death risk-ratio between persons of the above mentioned age groups

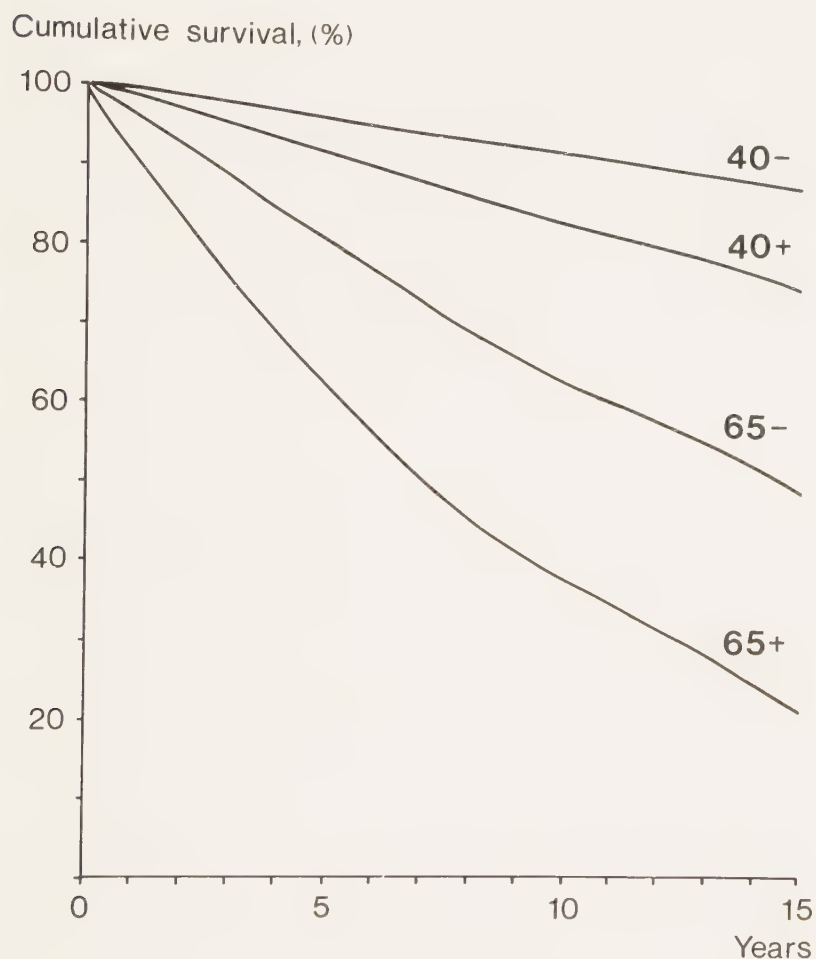


Figure 4. The influence of a clinical variable (locally advanced tumour; T3, UICC 1966) on survival according to the EORTC model. Survival curves are constructed for four hypothetical patients, aged 40 and 65 years, with (+) or without (-) this risk factor. As in the EORTC study adjustment for deaths in intercurrent disease is not performed.

was 8.5 for males and 10 for females. This would, in contrast to the EORTC report, suggest that age is less important as a risk factor for death in thyroid carcinoma than for overall death. Figure 3 shows that death in thyroid carcinoma only accounted for a minor part of the total number of deaths in the study group.

Figure 4 illustrates the survival curves according to the EORTC model tested on four hypothetical patients, aged 40 and 65 years, with or without a potential risk factor - locally advanced lesion (T3; UICC 1967). This figure displays a relatively small difference in survival between the younger patient with locally advanced disease and the patient 25 years older with a tumour confined to the thyroid, especially keeping in mind that survival is not adjusted for deaths in intercurrent disease. Thus, according to these figures, age at diagnosis can not be an important prognostic factor for differentiated thyroid carcinomas.

Extent of primary tumour

Irrespective of applied classification (T-stage according to UICC 1968 or AJCCS 1967, pT according to UICC 1978), the extent of the primary lesion in the present material was found to be an important independent predictor. As in the EORTC study, the stage was not as important as age at diagnosis, but testing the EORTC model according to Figure 4 or performing correction for death in intercurrent disease would give the opposite result. This has, however, been a controversial issue, since differentiated thyroid cancer is usually more advanced in elderly patients (25). Thus, Tscholl-Ducommun and Hedinger (5) found that the age was by no means the most important factor for papillary cancer, but they instead found that the prognosis correlated much better to the extent of the primary tumour.

Lymph node metastases

In analysis B (pretherapeutic factors; Table V.B), lymph node metastases were found to be one of the significant predictors. Neither in analysis A nor C were lymph node metastases of importance. The reason why lymph node metastasis seldom is considered as a negative, and sometimes as a positive, prognostic variable (2) in monofactorial analysis may be explained by its significant correlation to prognosticatively favourable factors, such as young age at diagnosis (Table IV) or histologic type (i.e. papillary carcinomas). However, in some reports where the age at diagnosis is taken into account, lymph node metastasis has been found to be a negative prognostic variable (3, 26). Another possible explanation for the differences in prognostic value might be different proportions of fixed lymph node metastases, which have a poor prognosis, as shown in monofactorial tests by Byar et al (6).

Distant metastases

The presence of distant metastases was also found to be an important prognostic variable, however of limited value, since differentiated thyroid carcinomas seldom have distant metastases at the time of diagnosis. The EORTC group found a difference in prognosis by dividing the patients with distant metastases into two groups with either single or multiple sites. The specific site of metastasis is, however, a more biologically appropriate and reliable predictor than the number of affected sites. Thus, other reports have shown that the prognosis of patients with lung metastases is much better than that of patients with bone metastases (27, 28).

Marked cellular atypia (MCA)

In analysis C (postsurgical analysis; Table V C) marked cellular atypia was shown to be one of the major prognostic factors for determining survival in differentiated carcinomas. A correlation was found between MCA and distant metastases ($p =$

0.054; Table IV). However, distant metastases were omitted in this analysis, due to the small number of patients (five) with this variable.

Figure 5 shows the survival curves, according to analysis C, applied on four patients, aged 40 and 65 years, with or without two of the potential risk factors (Table V C), viz: tumour-invasion beyond the thyroid capsule and MCA. This figure reveals that the outcome for the younger patient with these risk factors is worse than for the patient 25 years older without these, though survival is not adjusted for deaths in intercurrent disease.

Cumulative survival, (%)

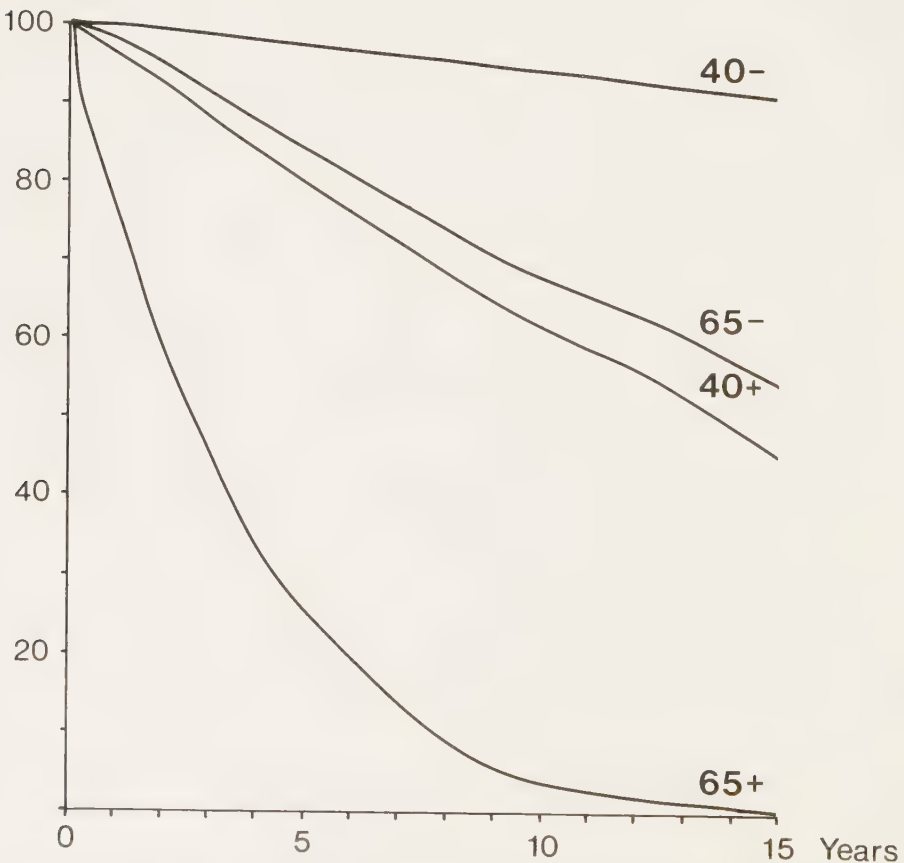


Figure 5. The influence of two postsurgical variables (pT4 according to UICC 1978 and marked cellular atypia) on survival. Survival curves are constructed for four hypothetical patients, aged 40 and 65 years, with (+) or without (-) these risk factors. Not adjusted for deaths in intercurrent disease.

The prognostic importance of MCA of differentiated thyroid carcinoma is in accordance with the observations from a study comprising 126 papillary carcinomas reported by Tscholl-Ducommun and Hedinger (5). They found a marked difference in death risk between well- and less differentiated papillary carcinomas ($p < 0.0005$). The present work was, however, started before this report was published, which explains some divergences in the principles of divisions. The MCA might reflect abnormal cellular DNA contents, which has recently been reported by Bäckdahl et al (29) to be an important predictor of survival of patients with papillary carcinoma. Concerning follicular carcinomas MCA is probably a much more important predictor than the growth-pattern of the tumour (viz: encapsulate or diffusely growing), but specific analysis for each histologic group is needed. MCA might also be an expression of an incipient transformation to an undifferentiated carcinoma (5). Results of many reports support the concept that differentiated carcinomas can be transformed to undifferentiated carcinomas (20, 30-32).

CONCLUSION

In contrast to the observations of the EORTC study neither sex nor age at diagnosis, when deaths in intercurrent disease were taken into account, were found to be important predictors for survival of patients with differentiated thyroid carcinomas with a long follow-up (median 11 years). The only two variables in the EORTC index which could be verified as important predictors in the present study (analysis A) were locally advanced disease and distant metastases. When testing other variables than those proposed by EORTC, marked cellular atypia (analysis C) was revealed to be an important predictor.

The results of the present investigation are in accordance with those of the study regarding papillary carcinomas by Tscholl-Ducommun and Hedinger (5), who stressed the prognostic importance of locally advanced and/ or less differentiated tumours. According to the present results old patients with differentiated thyroid carcinomas but without risk factors do not need any aggressive cancer treatment associated with higher morbidity.

Because the biologic behaviour of papillary, follicular and medullary carcinomas is different and certain microscopic attributes are specific for each histologic group, the prognostic factors ought to be analysed separately for each histologic group and separate prognostic indexes constructed.

APPENDIX 1

The EORTC prognostic index was based on a multivariate analysis of 507 patients originating from 23 various European hospitals and with a median follow-up of 40 months. A Weibull model was used. Age was included in the model as a continuous variable, the others were categorical. The prognostic index (PI) meant that the higher the sum of points, the worse was the survival. The scoring system was calculated according to the formula:

$$PI = A + 45 \cdot C + 15 \cdot M + 12 \cdot S + 10 \cdot T + 10 \cdot D$$

where A means age at diagnosis in years

C means anaplastic celltype (0 if absent, 1 if present)

M means distant metastasis (0 if none, 1 if single site, 2 if multiple sites)

S means sex (0 if female, 1 if male)

T means T-category (0 if T0, T1 or T2, 1 if T3)

D means medullary or follicular less-differentiated cancer (0 if absent, 1 if present)

APPENDIX 2

In short, Cox's proportional model may be described as

$$h_i(t) = L(t) \exp (\underline{B}' \underline{X}_i)$$

where $h_i(t)$ is the hazard (i.e. conditional probability of death in the period $(t+dt)$ given survival until t) at time t for the i :th patient, $L(t)$ represents an arbitrary base-line or nuisance hazard which does not need to be specified, $\underline{x}_i$ is a vector of covariates and $\underline{B}$ is a vector of regression coefficients to be estimated.

As $L(t)$ does not need to be specified, Cox's model is sometimes called semiparametric. A fully parametric model would assume that $L(t)$ followed some statistical distribution, say a Weibull distribution, and would hence be called a Weibull model. Cox's model is robust and insensitive to outliers in survival time because of its semiparametric construction.

The regression coefficients B give in their exponential form estimates of partial relative risk when related to different covariate studies.

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PROGNOSTIC FACTORS OF PAPILLARY
FOLLICULAR AND MEDULLARY
CARCINOMAS OF THE THYROID GLAND
Retrospective Multivariate Analysis
of 221 Patients with a Follow-up of 11 Years

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SUMMARY

Various prognostic factors have been tested in multivariate analyses of 421 patients with papillary, follicular or medullary thyroid carcinomas, in which the median follow-up time was 11 years.

Age and sex were not found to be significant predictors. Factors of importance were found to be for papillary carcinoma tumour invasion beyond thyroid capsule and marked cellular atypia, for follicular carcinomas tumour invasion beyond thyroid capsule, marked cellular atypia and distant metastases, and for medullary carcinomas tumour invasion beyond thyroid capsule only. Distant metastases were not evaluated for papillary and medullary carcinomas due to the limited number of cases.

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INTRODUCTION

Thyroid carcinomas constitute a heterogeneous group of tumours with widely varying prognoses. A large number of possible prognostic factors have been discussed for the papillary, follicular and medullary carcinomas occurring in the thyroid. They have, however, only been tested as independent predictors of survival in the great majority of studies found in the literature. It is well known that there is great co-variation between several of these variables, but only three studies have analysed the possible interdependence between different prognostic factors (Byar et coll. 1979; Warnebo et coll. 1981; Tennvall et coll. 1984).

One of these studies is a multivariate analysis of 507 patients by the EORTC Cooperative Group (Byar et coll. 1979), which, however, does not separately analyse the different histologic types. The median follow-up was also rather short (40 months). The study by Warnebo et coll. analysed some parameters for 153 patients with well-differentiated carcinomas with a longer period of follow-up. The justification of a long follow-up is that late recurrence of differentiated carcinomas is not unusual (Krisch et coll. 1980; Rougier et coll. 1983; Rossi et coll. 1980).

The multivariate analysis done in the third study (Tennvall et coll. 1984) tested the EORTC prognostic index on 221 patients with differentiated thyroid carcinomas who had a median follow-up exceeding 11 years. During this study, it was found desirable to make a separate multivariate analysis for each histological sub-group due to their different biological behaviour, but also due to certain microscopic qualities specific for each group. No such studies have been performed earlier, so far as is known to the authors.

The aim of the present study is therefore to separately identify variables for papillary, follicular and medullary carcinomas in order to predict the prognosis of survival for each histological group.

MATERIAL AND METHODS

Patient material

The material consists of 262 patients with histopathologically verified differentiated thyroid carcinomas referred to the Department of Oncology, University Hospital, Lund, during the years 1955-1972. The follow-up period was concluded in May, 1981. The median observation time was thus 11 years, and 26 % of the patients have been observed at least 15 years, which justifies the construction of survival curves up to 15 years. The female/ male ratio was 3/1. The median age was 49 years (range 8-83).

Primary assessment included radiologic examination of the lungs and the axial-skeleton, as well as a postoperative scintigraphy of the neck and a longitudinal scan of the whole body. If signs of metastases within two months after operation were demonstrated, distant metastases were considered as initially present.

Histopathologic examinations

Histologic material from 29 patients could not be found, it was thus possible to re-evaluate microscopic slides from only 233 patients. Excluded from further analysis were also: seven patients with tumours reclassified as benign, and five patients with distant metastases, due to incomplete information on the histopathologic feature of the primary tumour.

A total of 221 patients with differentiated thyroid carcinomas thus form the basis for this analysis. Differentiated thyroid carcinomas constituted 82 % of the histologically verified thyroid carcinomas referred to the department during this period.

All microscopic slides were re-examined by one and the same pathologist (MA).

Re-examination was performed on the original slides. There was great variation in number of slides from case to case. From some carcinomas, only one or two slides had been cut, from others eight to ten.

When the original slides were found to be of technically inferior quality, new slides were prepared from existing tissue blocks. The pathologist had no knowledge of the clinical course of the disease for each specific patient. The histologic re-classification was made according to the WHO histological typing of thyroid tumours (1974).

Seven patients initially classified as having follicular carcinomas were at re-examination classified as cases of follicular adenoma. The diagnosis of follicular carcinoma used the same criteria as have recently been described (Kahn and Perzin, 1983) that is evidence of invasion either into the capsule, into blood vessels, or into adjacent thyroid tissue, unless containing papillary structures. (Tumours previously classified as mixed papillary and follicular carcinoma were re-classified as papillary carcinomas since papillary carcinomas predominantly consisting of follicular structures were formerly most often described as follicular carcinomas.)

Papillary carcinomas were split up into three subgroups: tumours with 1) predominantly papillary architecture, 2) predominantly follicular architecture and 3) tumours consisting of equal proportions of papillary and follicular components (mixed type).

The concept of medullary carcinoma did not exist at the beginning of the study-period, and these tumours were then often classified as undifferentiated carcinomas of the thyroid.

Only 29 patients had an occult carcinoma (≤ 10 mm) of which 21 were papillary, 7 were follicular and one medullary. Eleven of the occult carcinomas were diagnosed due to lymph node metastases.

Analysed factors

Of the 221 patients, 142 had a papillary carcinoma, 53 a follicular carcinoma and 26 a medullary carcinoma.

The possibly prognostic histopathological variables analysed for all of the histological types were: non-occult tumour (tumours exceeding 10 mm in diameter); tumour invasion beyond the thyroid capsule (=pT4 according to UICC 1978); histopathologically verified lymph node metastases (pN+); invasion of vascular structures and the presence of marked cellular atypia (MCA) (Fig. 1, 2).

The group of papillary carcinomas were also analysed with regard to certain microscopic qualities, viz: the presence or absence of ground glass phenomenon and psammoma bodies.

For follicular carcinomas, the presence of Azkanazy cells and the absence of tumour capsule (follicular carcinoma diffusely growing, FCD) were studied. Follicular carcinomas were thus evaluated both as to capsular status and as to the cellular picture (MCA) (Fig. 2, 3).

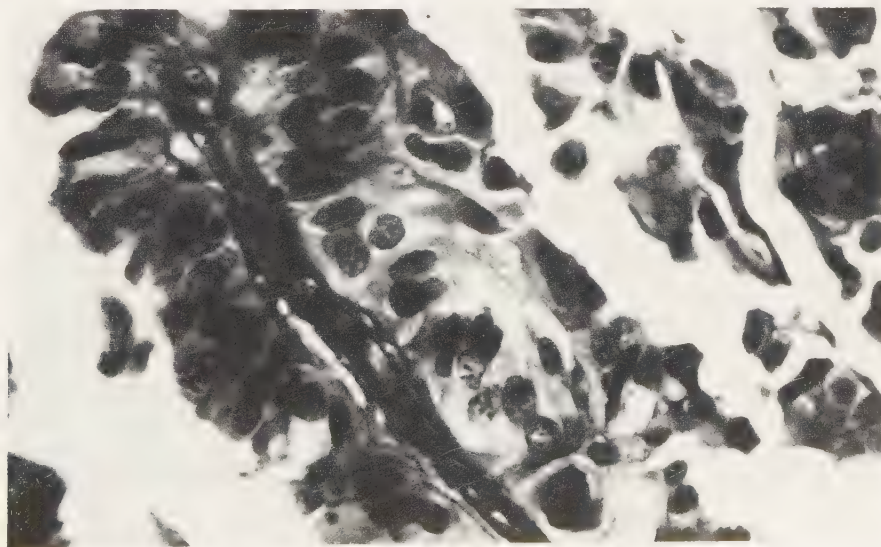


Fig. 1. A papillary carcinoma with marked cellular atypia. Different sized and irregular nuclei with uneven distribution of chromatin. No ground glass nuclei. HE x 500.

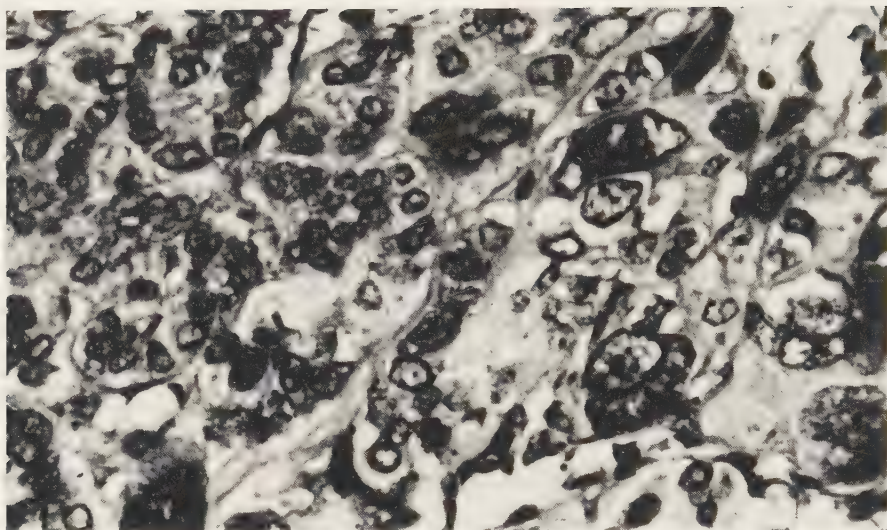


Fig. 2. A follicular carcinoma with marked cellular atypia. Considerable variation in cellular and nuclear size. Nuclei often irregular and hyperchromatic. HE x 500.

Distant metastases at diagnosis were confirmed in five patients: four patients with follicular carcinomas and one with papillary carcinoma. This parameter was only analysed for the follicular carcinomas.

The peroxidase-anti-peroxidase (PAP) method was not performed. Thus, the medullary carcinomas comprised carcinomas in which amyloid was seen. The majority of medullary carcinomas in the present study were diagnosed and treated before radioimmunoassay for human calcitonin was introduced in the clinical routine. No biochemically diagnosed occult medullary carcinomas were therefore included, nor was any evaluation of pretherapeutic plasma calcitonin-level as a prognostic tool attempted. It has furthermore not been possible to adequately distinguish familial from non-familial medullary carcinomas.

Because data regarding tumour invasion into blood-vessels in several patients with papillary carcinomas were not available, this parameter was omitted in the multivariate analysis. The same situation applies to pN+ in follicular carcinoma.

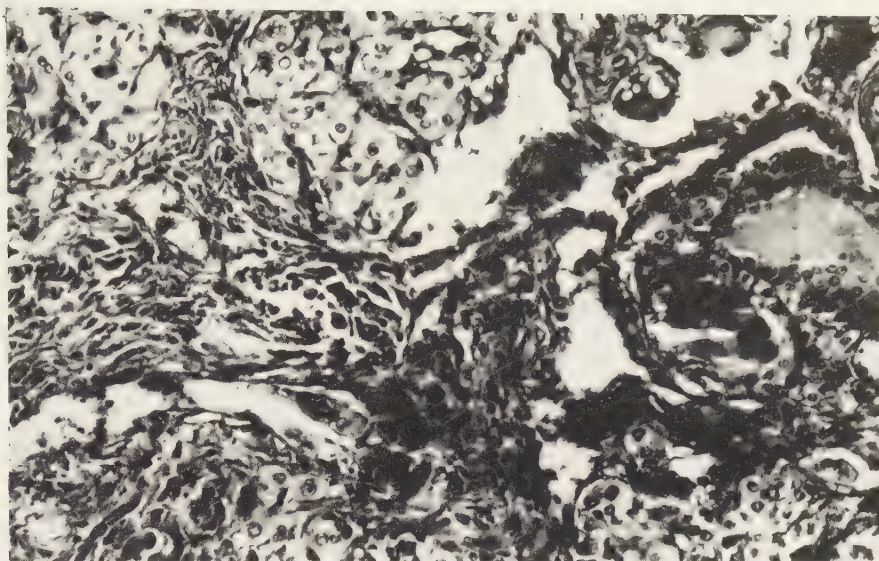


Fig. 3a. A follicular, non-encapsulated carcinoma without marked cellular atypia. The tumour infiltrates diffusely into benign thyroid tissue. HE x 160.

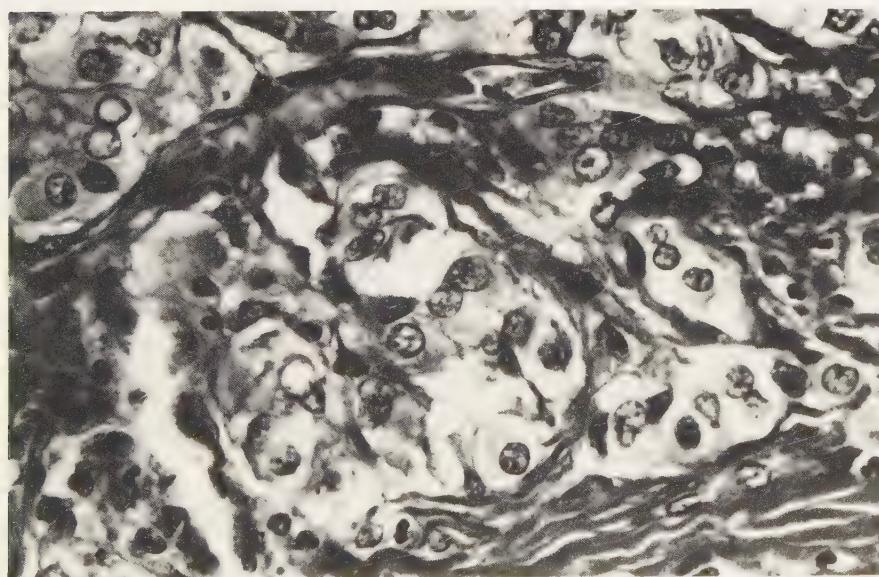


Fig. 3b. Higher magnification of the follicular carcinoma in Fig. 3a. The cellular atypia is slight. HE x 500.

Statistical methods

Survival was estimated by the actuarial method. Differences in cumulative survival between groups were tested by the Lee-Desu test (Lee and Desu, 1972).

Prognostic factors were assessed multivariately by Cox's proportional hazards model (Kalbfleish & Prentice, 1980).

Bivariate correlation between covariates was evaluated by Pearson's correlation coefficient. All p-values are two-tailed and p-values less than 5 % are referred to as significant.

Comparisons were made with national life table figures representative for a Swedish population with the same age and sex distribution as in the investigated group of patients in order to estimate death in intercurrent disease (Ederer et coll. 1961).

The calculations were made by the statistical packages SPSS and BMDP on a VAX 11/780 computer.

RESULTS

Survival by histologic type

The cumulative survival by the three histologic types of differentiated thyroid carcinomas for the whole patient material is shown in Fig 4. The outcome of the follicular carcinomas was significantly worse than that of papillary carcinomas ($p=0.009$). No other significant differences were found.

Cumulative survival, (%)

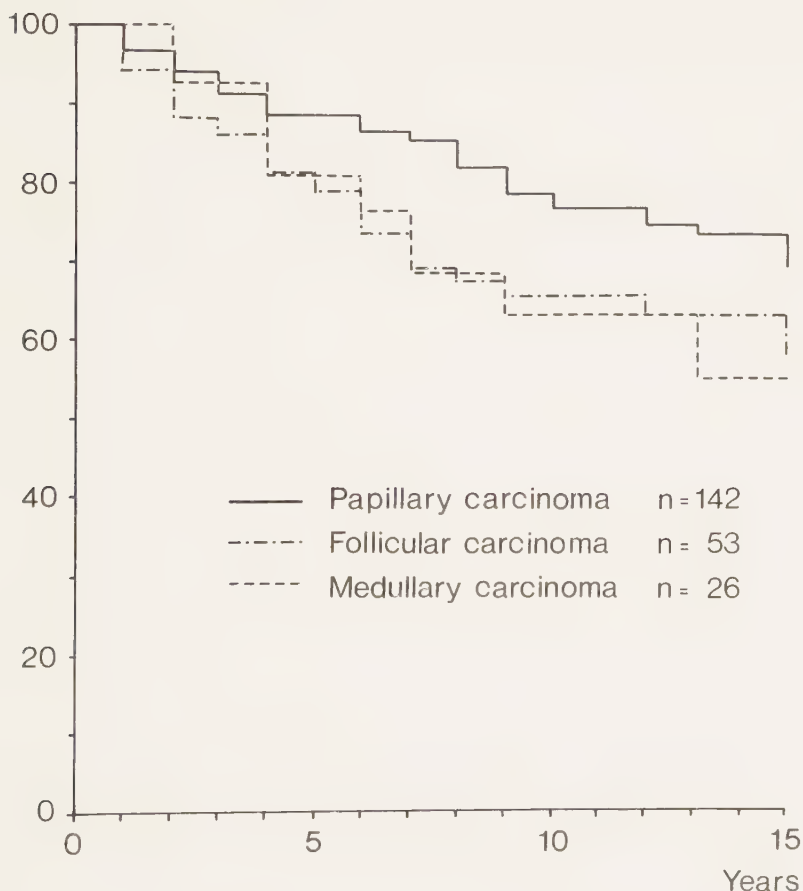


Fig. 4. Cumulative survival according to histologic type. A significant difference ($p=0.009$) is observed between papillary and follicular carcinomas.

When looking at the subgroups of papillary carcinomas with predominantly follicular components were found to have significantly better prognosis than the diffusely growing non-encapsulated follicular carcinomas ($p=0.037$). There was neither pairwise significant differences in survival between the papillary subgroups nor between the follicular subgroups.

We deliberately refrained from a further analysis of the three subgroups of papillary carcinomas because a quantitative evaluation of papillary structures is problematical since the distribution of these structures may vary considerably in different parts of the tumour (Tscholl-Ducommun & Hedinger, 1982) and since the number of slides showed a great variation from case to case in the present material.

Variables analysed for papillary, follicular and medullary carcinomas respectively have been tested as independent predictors of survival. The interactions between single variables and cumulative survival given in p-values are presented in Table 1.

Papillary carcinoma

The four significant predictors of survival in an univariate analysis of the 141 patients with papillary carcinoma were in the order of magnitude of relative risk: age at diagnosis, tumour invasion beyond the thyroid capsule (pT4), the presence of marked cellular atypia (MCA) and the absence of ground glass (Table 1).

Pair-wise correlations were calculated between all the possible negative prognostic factors for papillary carcinomas. The results are presented in Table 2. Several significant pair-wise correlations were found between the four important predictors of survival according to the univariate analysis. These correlations were: age at diagnosis and pT4 ($p<0.0005$); age and absence of ground glass ($p=0.002$); pT4 and MCA ($p=0.006$); pT4 and absence of ground glass ($p=0.006$); MCA and absence of ground glass ($p=0.034$); and age and MCA ($p=0.044$).

TABLE 1. Interaction between single variables for papillary, follicular and medullary carcinomas and cumulative survival given in p-values.

Variable	Papillary carcinoma (n=142)	Follicular carcinoma (n=53)	Medullary carcinoma (n=26)
Age	<0.00005	0.0009	0.0876
Male sex	0.6791	0.7595	0.4057
pT4 (UICC 1978)	0.0001	0.0024	0.0015
Non-occult tumour (>10 mm)	0.0711	0.4778	0.1293
pN+ (UICC 1978)	0.1481	0.9212	0.0118
Distant metastases (M+)		0.0343	
Diffusely growing non-encapsulated follicular carcinomas (FCD)		0.3116	
Marked cellular atypia (MCA)	0.0099	0.0120	0.0436
Groundglass	-0.0326*		
Psammoma bodies	0.2307		
Azkanazy cells		0.3656	
Vascular invasion	(0.58)**	0.2162	0.9246

* = Negative correlation.

**= Data not available for 31 patients.

The four prognostic factors were also found to be significantly correlated to other possibly prognostic factors. Age was strongly inversely correlated to lymph node involvement. Tumour invasion beyond the thyroid capsule was correlated to tumour size (>10 mm). The presence of ground glass was correlated to the presence of psammoma bodies and to the male sex.

Table 4 shows the outcome of the Cox proportional hazards model applied to the possible prognostic factors of papillary carcinoma. The significant prognostic variables were found to be the age at diagnosis and MCA.

TABLE 2. Pairwise correlations between possibly prognostic variables in 142 patients with papillary carcinoma. (p-values are given within brackets).

	Age	Male sex	>10 mm	pT4	pN+	MCA	Ground glass nuclei	Psamoma bodies
Age	-							
Male sex	-0.054 (0.260)	-						
Non-occult tumour (>10 mm)	0.030 (0.364)	-0.100 (0.119)	-					
Tumour invading beyond thyroid capsule (pT4)	0.282 (<0.0005)	0.043 (0.306)	0.234 (0.003)	-				
Lymph node involvement (pN+)	-0.353 (<0.0005)	0.162 (0.027)	-0.023 (0.393)	0.046 (0.295)	-			
Marked cellular atypia (MCA)	0.144 (0.044)	0.050 (0.277)	-0.011 (0.448)	0.210 (0.006)	0.042 (0.309)	-		
Ground glass nuclei	-0.241 (0.002)	0.203 (0.008)	-0.119 (0.080)	-0.211 (0.006)	0.045 (0.298)	-0.154 (0.034)	-	
Psamoma bodies	-0.0004 (0.498)	0.127 (0.066)	-0.048 (0.287)	-0.024 (0.390)	0.200 (0.009)	0.090 (0.144)	0.254 (0.001)	-

- = Negative correlation.

TABLE 4. Significant negative prognostic variables for survival of papillary, follicular and medullary carcinomas. Multivariate statistical analysis.

Histologic type	Negative prognostic factor	Relative risk	Coefficient*	p-value	Occurrence
Papillary carcinoma n=142	Age at diagnosis	10.60**	0.0944	<0.00005	
	Marked cellular atypia	4.35	1.4721	0.0361	4 %
Follicular carcinoma n=53	Age at diagnosis	9.44**	0.0949	<0.00005	
	Marked cellular atypia	6.81	1.9180	0.0007	26 %
	Distant metastases	3.96	1.3771	0.0698	8 %
Medullary carcinoma n=26	Tumour with invasion beyond thyroid capsule =pT4	6.31	1.8416	0.0071	23 %

* = Coefficient for survival function.

** = A death-risk ratio between a person of 65 years and 40 years of age at diagnosis.

To illustrate the model (Table 4), the relative death-risk between two patients with papillary carcinomas has been estimated; one aged 65 at diagnosis, with a tumour showing a histopathologic pattern of MCA, and one aged 40 at diagnosis, with papillary carcinoma without MCA. This factor is 46 times (10.60×4.35) greater for the older patient.

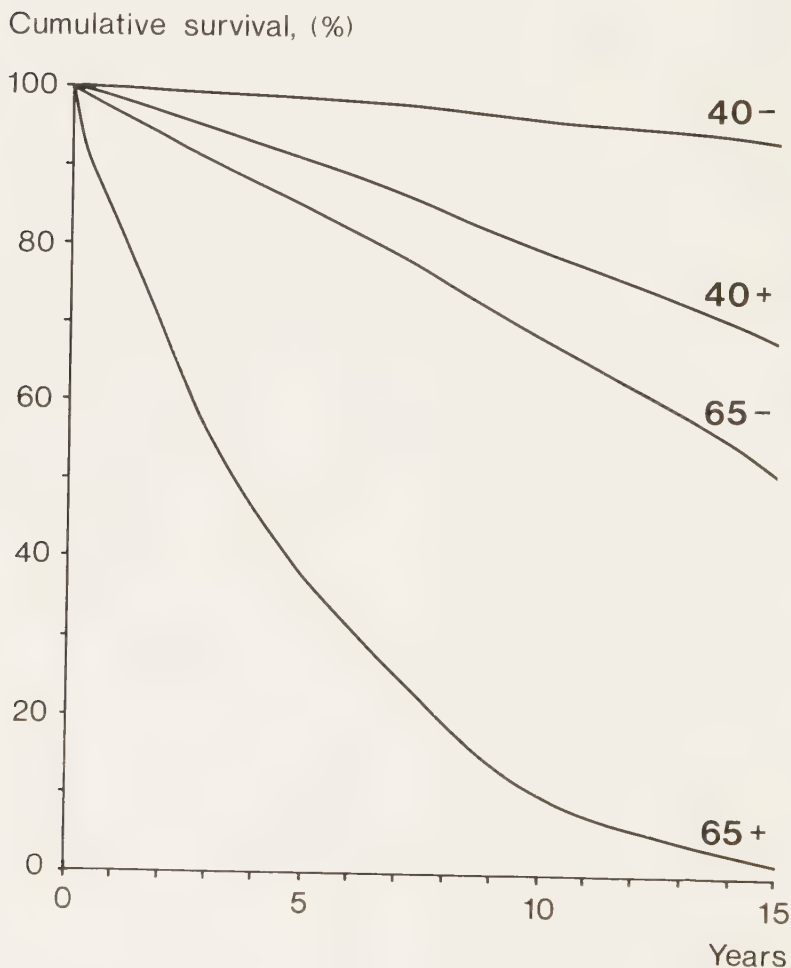


Fig. 5. Survival curves according to the applied multi-variate model for papillary carcinoma, constructed for four hypothetical patients with (+) or without (-) two possible risk factors, MCA and pT4. Survival is not corrected for deaths in intercurrent disease.

The multivariate analysis also confirmed that there was a significant correlation between age and pT4, and between age and the absence of ground glass. The prognostic importance of age at diagnosis might be explained by a significant correlation to factors of real importance for survival; hence, pT4 and the absence of ground glass were tested according to Figure 5. This figure illustrates the survival according to the applied multivariate model, constructed for four hypothetical patients with papillary carcinoma, aged 40 and 65 years, with or without two potential risk factors, viz: MCA and pT4. The figure illustrates the small difference in survival between the younger patient with these two risk factors and the 25 year older patient without these two risk factors. The absence of ground glass was also tested, but it did not contribute to the clinical course of the disease.

On the basis of these observations, a hypothetical model has been constructed (Fig. 7) describing the relationship between the most important negative prognostic variables of survival for patients with papillary carcinomas.

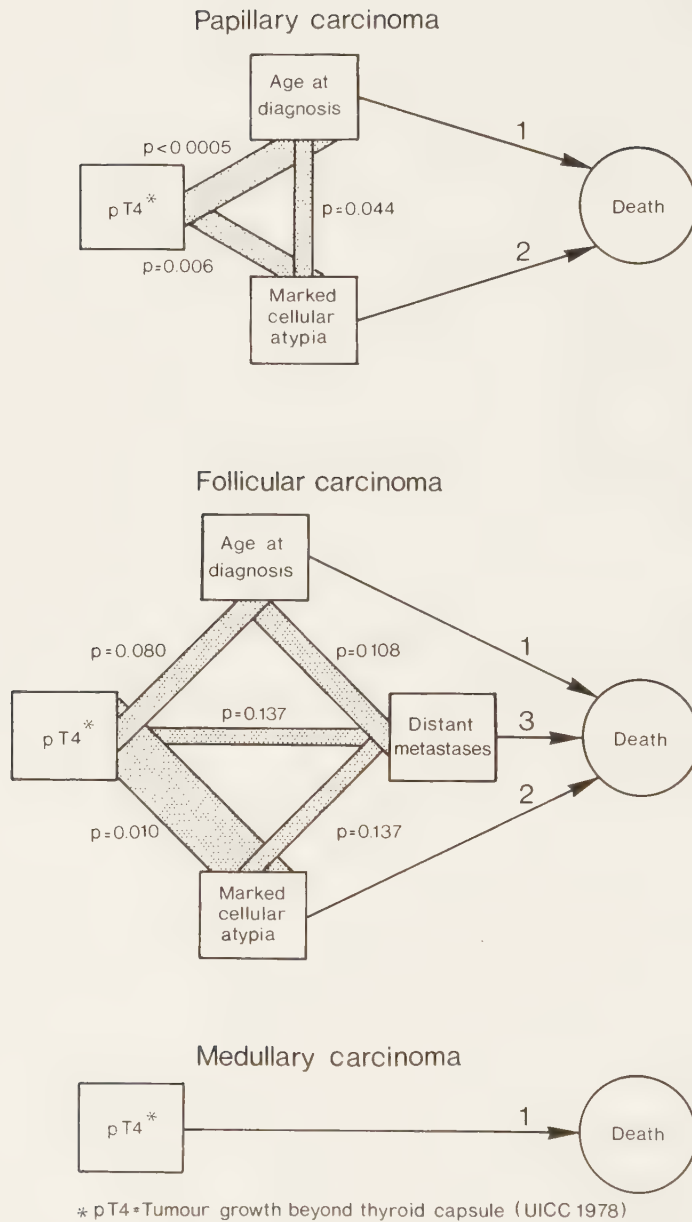


Fig. 7. Hypothetical model of correlations between the most important predictors for a patient with papillary carcinoma, follicular carcinoma and medullary carcinoma.

Follicular carcinoma

Four variables showed a strong interaction with cumulative survival in 53 patients with follicular carcinoma according to the univariate analysis (Table 1). These were in their order of magnitude of relative risk: age at diagnosis, pT4, MCA, and distant metastases.

The results of the pair-wise correlation between all the possibly negative variables for follicular carcinomas are presented in Table 3. The only significant pair-wise correlation among the four above-mentioned variables was found between MCA and pT4 ($p=0.010$). Non-encapsulated, diffusely growing tumours (FCD) showed a significant association with pT4, and a weaker association to distant metastases, to the presence of Azkanazy cells and to tumour size. A significant correlation was also found between age and the presence of Azkanazy cells. Males proved to be younger at diagnosis than females.

The results of the multivariate analysis (Table 4) indicated that age at diagnosis, MCA and distant metastases were the important factors for survival.

The same two patients in the example above, but applied on follicular carcinomas, would give a death-risk ratio 64 (9.44×6.81) times higher for the older patient.

Since the variable pT4 showed a significant correlation to cumulative survival ($p=0.0024$) in the monofactorial analysis (Table 1), the importance of this factor in conjunction with MCA was evaluated in relation to age at diagnosis. Figure 6 demonstrates the survival curves according to the multivariate model constructed for four hypothetical patients, aged 40 and 65, with or without these two variables. This figure shows that there is no difference in survival between the younger patient with these two risk factors and the 25 year older patient, though adjustments for deaths in intercurrent disease was not performed.

TABLE 3. Pairwise correlations between possibly prognostic variables in 53 patients with follicular carcinoma. (p-values are given within brackets).

	Age	Male sex	>10 mm	pT4	pN+	M+	FCD	MCA	Az+	Vascular invasion
Age	-									
Male sex	-0.224 (0.054)	-								
Non-accult tumour (>10 mm)	-0.068 (0.314)	0.176 (0.103)	-							
Tumour invading beyond thyroid capsule (pT4)	0.196 (0.080)	0.071 (0.307)	-0.019 (0.446)	-						
Lymph node involvement (pN+)	0.017 (0.453)	0.156 (0.133)	-0.037 (0.398)	0.191 (0.085)	-					
Distant metastases	0.108 (0.221)	-0.129 (0.178)	0.112 (0.213)	0.153 (0.137)	0.123 (0.189)	-				
Follicular carcinoma, diffusely growing (FCD)	0.033 (0.409)	0.010 (0.473)	0.229 (0.049)	0.425 (0.001)	0.168 (0.115)	0.326 (0.009)	-			
Marked cellular atypia (MCA)	0.029 (0.419)	-0.043 (0.380)	0.107 (0.222)	0.321 (0.010)	0.056 (0.345)	0.153 (0.137)	0.080 (0.285)	-		
Azkanazy cells (Az+)	0.297 (0.015)	-0.050 (0.360)	0.165 (0.120)	-0.014 (0.462)	0.016 (0.456)	-0.121 (0.195)	-0.263 (0.029)	-0.133 (0.171)	-	
Vascular invasion	0.027 (0.424)	0.162 (0.124)	0.212 (0.063)	0.214 (0.062)	0.128 (0.181)	0.102 (0.234)	0.073 (0.303)	0.214 (0.062)	-0.182 (0.096)	-

- = Negative correlation.

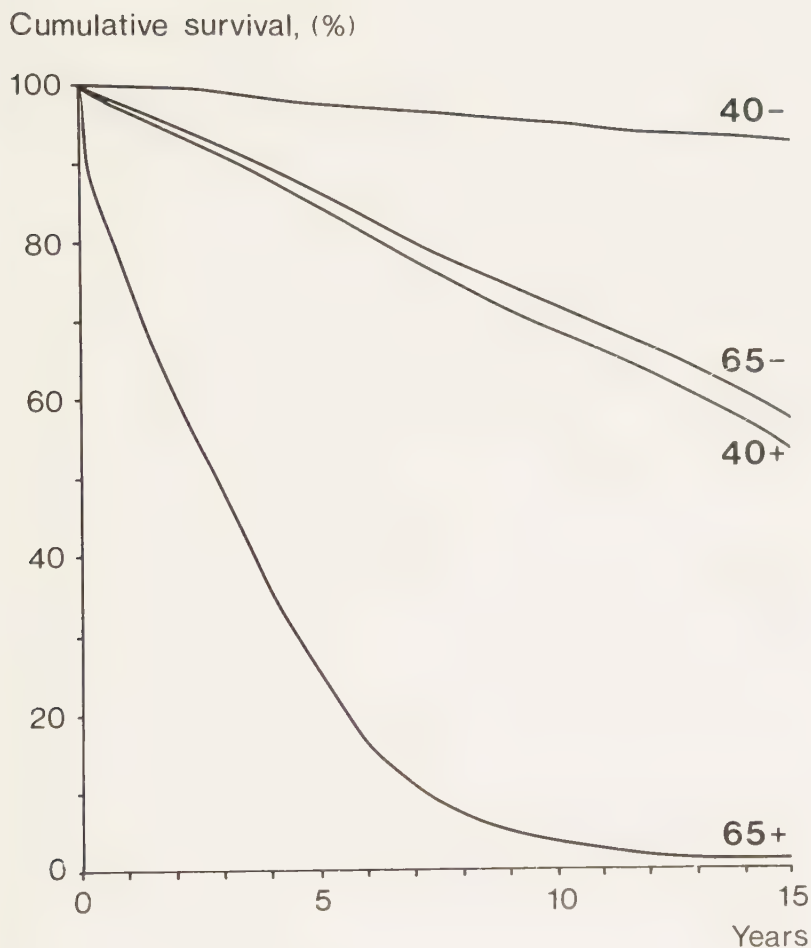


Fig. 6. Survival curves according to the applied multivariate model for follicular carcinoma, constructed for four hypothetical patients with (+) and without (-) two possible risk factors, MCA and pT4. Survival is not corrected for deaths in intercurrent disease.

The multivariate analysis confirmed the significant correlation between pT4 and MCA.

Figure 7 summarizes the correlations between important negative prognostic factors based on the results described.

Medullary carcinoma

According to the univariate analysis regarding cumulative survival of medullary carcinomas (Table 1) three significant predictors were found. These were in their order of magnitude of relative risk: pT4, pN+ and MCA.

The variable pT4 showed a significant correlation both to pN+ ($p<0.0005$), and to MCA ($p=0.030$). A significant correlation was found between male sex and MCA ($p=0.024$). The outcome of the multivariate analysis (Table 4 and Fig. 7), applied to the factors investigated, indicated that pT4 was the only important prognostic factor.

The age at diagnosis was thus not found to be an important prognostic negative factor for survival in cases of medullary carcinoma.

Estimations of deaths in intercurrent disease

Since the group of patients who had undergone surgery entered the study at admission to the Department of Oncology for additional therapy or for follow-up, no deaths from surgical complications were encountered. There were neither any deaths from treatment complication nor any over-representation of deaths from other malignant diseases. The area between the two curves in each of Figures 8 A, B and C therefore represents deaths in papillary, follicular and medullary carcinomas, respectively.

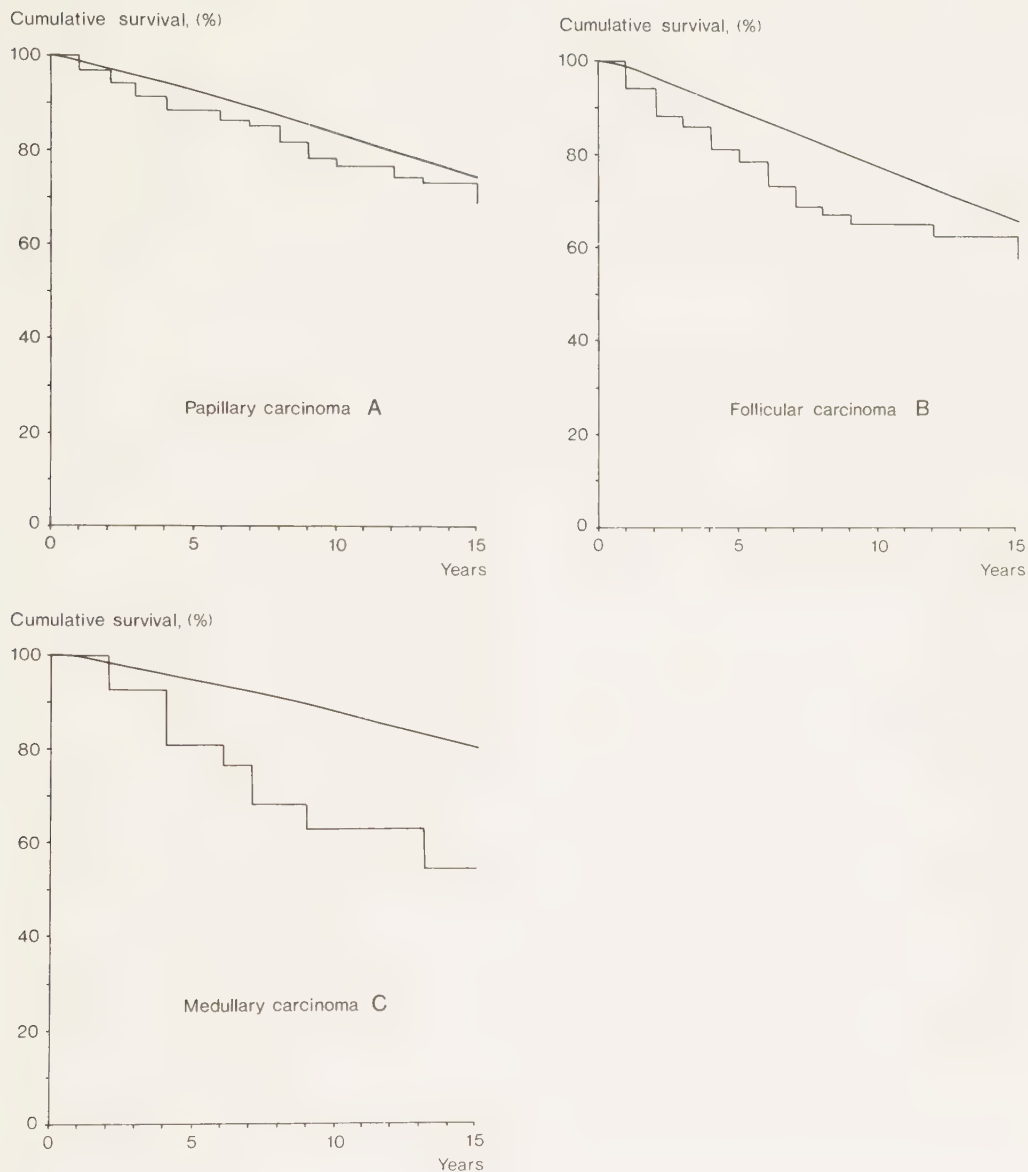


Figure 8.

Crude survival of the 142 patients investigated with papillary thyroid carcinoma (A), the 53 patients with follicular carcinomas (B) and the 26 patients with medullary carcinomas (C), compared to the survival in an age- and sex-matched Swedish population. The area between this curve and curves A, B and C indicates death from the different types of thyroid carcinoma.

DISCUSSION

The conflicting results found in various reports on the prognosis of differentiated carcinomas of the thyroid gland can to a great extent be explained by the fact that, in the majority of these reports, the covariations between several of the most important prognostic factors have not been taken into account.

A simultaneous control of variables with potential prognostic value is therefore of importance. This can be done with multivariate analysis. Prognostic factors of differentiated thyroid carcinoma have hitherto only been assessed with multivariate analysis by Byar et coll.(1979), Warnebo et coll. (1983) and Tennvall et coll.(1984).

None of these reports have, however, evaluated the prognostic factors of papillary, follicular and medullary carcinomas in separate analyses. Due to the differing biologic behaviour of these three histologic groups of differentiated thyroid carcinomas, and due to the specific microscopic qualities of those of possible prognostic importance, it is probably more appropriate to evaluate the prognostic factors for each histologic group separately. These assumptions were also supported by investigations of the crude survival for the papillary, follicular and medullary carcinomas studied in this report compared to survival in an age- and sex-matched Swedish population (Fig. 8). A much more benign course of papillary carcinomas was demonstrated in comparison to follicular and medullary carcinomas.

Since therapy has not been included in the analysis, it is possible that the effects of therapy, if taken into account, might alter the importance of some prognostic variables.

Papillary carcinoma

The multivariate analysis of papillary carcinomas revealed that the only two major determinants for survival were the age at diagnosis and marked cellular atypia (Table 4). There was only a weak correlation ($p=0.44$) between these two major prognostic factors, indicating their relative reciprocal independence.

MCA was found, however, to be an unusual characteristic of papillary carcinoma, occurring in only 4 % of this histologic group (Fig. 1). MCA might reflect abnormal DNA-content in individual cells, which has recently been demonstrated as being an important predictor of survival in papillary carcinoma (Bäckdahl et coll. 1983); it might also be an expression for an incipient transformation to an undifferentiated carcinoma (Tscholl-Ducommun & Hedinger, 1982).

The other principal prognostic variable of importance, age at diagnosis, was found to be significantly correlated ($p<0.0005$) to tumour-invasion beyond the thyroid capsule (pT4) and to the absence of ground glass ($p=0.002$). There was also a significant correlation ($p=0.006$) between these two factors.

As the age at diagnosis not only contains prognostic information on the tumour, but also prognostic information on intercurrent diseases, there is always a risk of overestimating the importance of age, especially when the malignant disease has a protracted course. It is therefore necessary to analyse the role of these age-correlated factors. The importance of the age at diagnosis was explained by its significant correlations to pT4. When adjustments were made for pT4 and MCA (Fig. 5), the remaining differences in survival only reflected deaths in intercurrent diseases. When pT4 and MCA were thus taken into account, other variables did not add further prognostic information.

This is in accordance with observations made by Tscholl-Ducommun & Hedinger (1982). They found that the prognosis

of papillary carcinoma correlated significantly better with the local extension of the primary tumour than with the age at diagnosis. These findings are also in agreement with other reports on papillary carcinomas (Franssila 1978; Krisch et coll. 1980).

According to Franssila (1975), age had a minor effect on survival within any histologic type and stage of the disease. A number of studies have, however, demonstrated the prognostic significance of age in papillary as well as in follicular carcinomas (Cady et coll. 1979; Fraumenhofer et coll. 1979; Mazzaferri & Young 1981). All these reports were, however, based only on mono- or bi-factorial survival analysis. The multivariate analysis by the EORTC-group (Byar et coll. 1979) also found the age at diagnosis to be the most important predictor of survival. In this study, however, all types of histology of thyroid cancer were pooled together, even the anaplastic giant and spindle cell carcinomas. No adjustments were made for death in intercurrent disease, and the age at diagnosis was not analysed further with respect to the influence of strongly age-correlated factors on survival.

It is nevertheless well known that elderly patients with papillary thyroid cancer more often have locally advanced tumours (Proye et coll. 1981). This correlation might be due to a longer patient's and/or doctor's delay in the elderly patient groups. This hypothesis will be further investigated.

A further argument against the EORTC-thesis are the occult papillary carcinomas which have an excellent prognosis irrespective of age (Hubert et coll. 1980; Mazzaferri et coll. 1981; Bondesson et coll. 1981; Tscholl-Ducommun & Hedinger 1982). Only a few cases of occult papillary carcinomas with poor prognoses have been reported (Beaugié et coll. 1976; Fraumenhofer et coll. 1979; Patchefsky et coll. 1979).

Franssila (1978) found that blood vessel invasion was an important predictor for survival, but the proportions of papillary and follicular structures were not such factors.

These two parameters have, however, only been studied monofactorially in the present study, and no prognostic importance was found.

Follicular carcinoma

The multivariate analysis applied on follicular carcinomas demonstrated that the three factors associated with significant impairment of survival in their order of priority were: the age at diagnosis, marked cellular atypia and distant metastases (Table 4 B).

MCA occurred in 26 per cent of all follicular thyroid carcinomas (Fig. 2). The effect of age on survival was not found when adjustments were made for pT4 and MCA (Fig 6). The prognostic information could thus be restricted to three of the investigated variables, viz: pT4, MCA and distant metastases (Fig 7). These observations are in contradiction to a study by Young et coll. (1979), who found that the only deaths directly attributable to follicular carcinoma occurred in patients with distant metastasis at the time of presentation. According to Ladurner et coll. (1982), however, the mortality risk is high during the initial four years after operation, but during this period the course of the disease is the same for patients with or without distant metastases.

In contrast to several other reports (Franssila 1975; Ladurner et coll. 1983) no prognostic difference could be found between the encapsulated sub-type of follicular carcinoma and the diffusely infiltrating sub-type ($p=0.312$) (Fig. 3). The other aspect of the differentiation of follicular carcinomas, viz: marked cellular atypia (Fig 2), proved instead to be a much more important prognostic factor ($p=0.012$).

According to several reports (Woolner et coll. 1971; Meissner & Warren 1969), the prognosis of follicular carcinoma depends on the extent of vascular and capsular invasion at the time of surgical excision. In the present report, it was, however,

not possible to make a quantitative comparison between different tumours due to the varying number of histopathological sections.

The presence of Askanazy cells in follicular carcinomas did not influence their clinical course. Several authors (Thompson et coll. 1974; Samaan et coll. 1983) claim that Askanazy-cell carcinomas had poor prognoses, whereas Staunton & Skeet (1979) asserted that they were less malignant than other follicular carcinomas.

Medullary carcinoma

Multivariate analysis of medullary carcinomas showed that the only prognostic factor negatively influencing survival was extrathyroidal disease (pT4) at presentation (Table 4; Fig 7). The prognostic importance of local extension has also been asserted in other reports (Chong et coll. 1975; Rossi et coll. 1980; Wells et coll. 1982). In most patients there is a positive correlation between plasma calcitonin and the measured thyroid tumour mass at the time of surgery (Wells et coll. 1982), but, in a few patients with tumours showing cellular heterogeneity, there is a discordance between tumour size and plasma calcitonin (Lippman et coll. 1982).

Age has also been asserted to be an important predictor of the course of medullary carcinomas (Chong et coll. 1975; Rossi et coll. 1980). In the present report, however, age at diagnosis was neither correlated to a poor prognosis nor to a locally advanced disease (Fig. 7). According to these observations, the prognostic index of EORTC (Byar et coll. 1979) is thus not at all applicable to medullary carcinoma.

Woolner et coll. (1971) reported that the prognosis of medullary carcinoma appeared to depend to a considerable extent on the presence or absence of nodal metastases. This trend was also seen in the present study, but only in the monofactorial test (Table 1).

Marked cellular atypia was an unusual characteristic of medullary carcinoma in the present study (3 patients) and it was not found to influence the clinical course of the disease. Due to the small number of patients with this characteristic, the results must be interpreted with caution. However, Lippman et coll. (1982) showed with immunoperoxidases staining of calcitonin that cellular heterogeneity in the tissue of medullary carcinoma was associated with a grave prognosis.

CONCLUSION

According to multivariate analyses, and when the influence of deaths in intercurrent disease was estimated, the age at diagnosis was not found to be an important predictor of survival in any of the three histologic groups of differentiated thyroid carcinomas, i. e. papillary, follicular or medullary carcinomas. The patient's sex did not show any prognostic importance in any histologic group. Distant metastases at diagnosis could not be evaluated for papillary and medullary carcinomas due to the small number of patients with this characteristic.

For papillary carcinomas, tumour invasion beyond thyroid capsule and marked cellular atypia proved to be important predictors.

For follicular carcinomas, tumour invasion beyond thyroid capsule, marked cellular atypia and distant metastases were important for their outcome.

For medullary carcinomas, tumour invasion beyond thyroid capsule was the only parameter of importance.

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